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BLOOD PYRUVATE ESTIMATIONS IN THE DIAGNOSIS AND TREATMENT OF POLYNEURITIS

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POLYNEURITIS, as seen in this country, is usually of obscure ætiology. A small percentage of cases respond to treatment with vitamin B_1: and give a history of dietary deficiency of this vitamin. In these cases the biochemical derangement responsible for the polyneuritis is known, the outstanding defect being an impairment of the normal metabolism of pyruvate, formed as an intermediary in the breakdown of glucose. Thus, it was shown *in vitro* by Peters and Thompson (1934) that more pyruvate accumulates in preparations of respiring brain tissue from avitaminous pigeons than in similar preparations of normal brain, and that this extra accumulation can be prevented by the addition of small amounts of thiamine hydrochloride to the brain preparations. The blood pyruvate level was later found to be raised in thiamine-deficient pigeons and rats by Thompson and Johnson (1935) and in acute beri-beri in man by Platt and Lu (1939). Peters (1936) concluded that thiamine acts as a co-enzyme, or part of a co-enzyme, of the pyruvate oxidase system. Deficiency of this vitamin results therefore in a block in the series of energy-yielding reactions whereby glucose is oxidized by the cells; its breakdown proceeds as far as pyruvic acid which, since its further oxidation is inhibited, consequently accumulates. The importance of the pyruvate oxidase system lies in the fact that utilization of oxygen by most tissues is dependent on its integrity, and failure of this system results in virtual tissue anoxia.

Inhibition of pyruvate oxidation by thiamine deficiency can therefore give rise to polyneuritis. But inhibition of the pyruvate oxidase system can be caused in other ways. For example, interference with a protein component of the system has been shown to underlie the toxic action of arsenic on living cells (Peters, Sinclair and Thompson, 1946), and it

is of interest in this connexion to recall the points of clinical resemblance which have long been recognized between arsenical neuritis and the neuritis of dry beri-beri (Ross and Reynolds, 1901). It is now known that arsenic reacts with thiol groups in the protein molecule, and it is as a result of this interaction that the blood pyruvate level is significantly raised in animals poisoned with sodium arsenite, and also in cases of post-arsphenamine intoxication in man (Sexton and Gowdey, 1947). Certain other metal derivatives also bring about inhibition of pyruvate oxidation; thus, Thompson and Whittaker (1947) showed that compounds of gold, mercury and antimony (including some of the organic therapeutic preparations such as "myocrisin" and "stibophen") can inhibit brain pyruvate oxidase preparations.

As a further example in man of inhibition of a protein component of the pyruvate oxidase system, evidence has recently been obtained of a defect in pyruvate oxidation in epidemic dropsy in India, resulting from the accidental consumption of argemone oil. Sarkar (1948) isolated a toxic alkaloid sanguinarine from argemone oil, which he found to inhibit the pyruvate oxidase system. He also found the blood pyruvate raised in rats poisoned with this substance, a finding which agrees with the earlier observations of Wilson and Ghosh (1937) that a rise in the bisulphite-binding capacity of the blood (and presumably therefore of the blood pyruvate) occurs in cases of epidemic dropsy in man.

There are, therefore, a number of toxic agents which, if they gained access to the body, could bring about a biochemical lesion resembling that occurring in thiamine deficiency, although resulting from a different underlying mechanism; in the one case the missing vitamin causing a deficiency of the essential co-enzyme for pyruvate oxidation, and in the other the toxic agent inhibiting this oxidation by its interaction with a protein component of the enzyme system. For this reason it seemed of interest to study the pyruvate metabolism in an unselected group of patients with polyneuritis. If evidence of impaired pyruvate metabolism could be found in patients having an adequate intake of thiamine it would suggest that inhibition of a thiol protein component might be concerned, and that it might be of value to attempt treatment with BAL (2:3-dimercaptopropanol or Dimercaprol) a substance which has proved effective in the treatment of different forms of metallic poisoning. This dithiol is capable of forming a more stable compound with the metal or metal-containing molecule than that formed by the thiol protein of the pyruvate oxidase system (*see* Peters, Stocken and Thompson, 1945). Furmanski (1948) has already described the successful treatment of 4 cases of "toxic" polyneuritis with BAL, but he did not report the blood pyruvate levels in the cases studied.

Determination of the fasting blood pyruvate level does not, however, provide an adequate test for revealing minor or even moderate degrees of thiamine deficiency, such as might be expected to occur in this country. Thus, even in oriental beri-beri, although Platt and Lu (1939) found very significant elevations of the blood pyruvate level in the acute type of the disease, in the subacute condition the values found were within normal limits or only slightly raised. In America, Bueding, Wortis and Stern (1942) reported elevated fasting values in "acute peripheral neuropathy" and in certain febrile conditions, but normal values in "chronic peripheral neuropathy." A more sensitive test is provided by estimation of the blood pyruvate level after subjecting the individual to a "loading" dose of glucose. This was first shown in man by Bueding, Stein and Wortis (1941) who found that the elevation of the blood pyruvate level brought about by the ingestion of glucose was greater and more prolonged in thiamine-deficient subjects ("acute peripheral neuropathy" associated with chronic alcoholism and Wernicke's syndrome) than in normally nourished persons. In studies of induced thiamine deficiencies Elsom, Lukens, Montgomery and Jonas (1940) and Williams, Mason, Power and Wilder (1943) have reported that while the fasting blood pyruvate level is only occasionally raised, it is regularly increased after the oral administration of glucose.

We therefore studied a series of cases of polyneuritis using as our index of the state of pyruvate metabolism the "pyruvate tolerance test" described by Williams *et al.* (1943). Since glucose and not sodium pyruvate is used as the loading substance before serial blood pyruvate estimations, it is, perhaps, by analogy with the glucose tolerance test, not strictly a test of the pyruvate tolerance; since it provides information concerning the ability of the body to metabolize the pyruvate formed from the ingested glucose it is proposed to call it a "pyruvate metabolism test."

After determining, by means of this test, whether any given case showed a disturbance of pyruvate metabolism, we have attempted to assess the value of controlled therapy, and to discover whether the metabolic lesion was brought about by a deficiency of the co-enzyme or by an inactivation of the enzyme. The test was therefore repeated after a period of parenteral thiamine administration on a massive scale; if the pyruvate metabolism appeared then to have returned to normal, thiamine therapy was continued in the hope of obtaining eventual clinical improvement. If, on the other hand, pyruvate metabolism was still impaired, BAL therapy was commenced and the test repeated after a full course of injections of this drug.

A preliminary account of the application of this metabolic test to cases of suspected dietary deficiencies and of metallic poisoning, and also

to a small series of cases of polyneuritis, has already been published (Joiner, Thompson and Watson, 1950).

In view of certain suggestions that have been made, a secondary purpose of the work described in this paper has been to assess the value of determinations of the blood lactate-pyruvate ratio in the diagnosis of thiamine deficiency and of other conditions affecting the pyruvate oxidase enzyme system. In the absence of oxygen pyruvate is largely converted into lactate, both substances accumulating in both tissues and blood. In anoxia the increase in the blood lactate is considerably greater than that of pyruvate, and the ratio of lactate to pyruvate has been used as a measure of tissue oxidation (Friedemann, Haugen and Kmieciak, 1945). In thiamine deficiency in rats and pigeons on the other hand, Stotz and Bessey (1942) found that, as compared with anoxia, the blood pyruvate level was increased by a relatively greater amount than the lactate, and that the lactate-pyruvate ratio was reduced. Keys, Henschel, Taylor, Mickelsen and Brozek (1945) found a rise in the blood pyruvate without any increase in the blood lactate during experimentally induced thiamine deficiency in man, but the change although statistically significant was small in amount. Goldsmith (1948) also found the mean blood lactate-pyruvate ratio in a group of patients with thiamine and riboflavin deficiencies to be significantly lower that that of a normal control series, and she suggested that this ratio might be useful in the assessment of thiamine deficiency. In some of the cases studied by us we have therefore compared the results of the pyruvate metabolism test with the lactate-pyruvate ratio.

Experimental Details

Methods.—A standard procedure modified from that of Williams *et al.* (1943) has been adopted, and is performed upon the fasting subject resting in bed. The patient is given two doses by mouth of 50 grammes of glucose, each dissolved in about 200 ml. of water, at 0 and 30 minutes, and 3 ml. samples of venous blood are withdrawn at 0, 60 and 90 minutes for determination of pyruvate level. In the earlier patients studied, a sample was also taken at 30 minutes, but this was later abandoned as it was found that no useful information was obtained by analysis of so early a sample. It is important to collect the blood with the minimum of venous stasis, and in order to exclude any possible effects of localized muscular exertion no clenching and unclenching of the hand is allowed before collection.

Pyruvic acid was determined by the method of Friedemann and Haugen (1943) and lactic acid by the method of Barker and Summerson (1941).

Clinical material.—In order to obtain our own values for the "normal" levels of blood pyruvate under the conditions of this test, it has been carried out on 50 control subjects comprising 12 healthy young adults with ages ranging from 18–30, and 38 hospital patients with ages varying from 18–75 suffering from conditions in which there was no reason to expect abnormal pyruvate metabolism. 40 cases of polyneuritis, radiculitis and myelopathy have been studied, and, for reasons mentioned later, tests have also been performed on 8 patients with thyrotoxicosis, 9 healthy normal pregnant women and 10 cases of congestive heart failure.

Results

Control Subjects

Table I gives results of the pyruvate metabolism test on the control series of subjects (*see* also fig. 1).

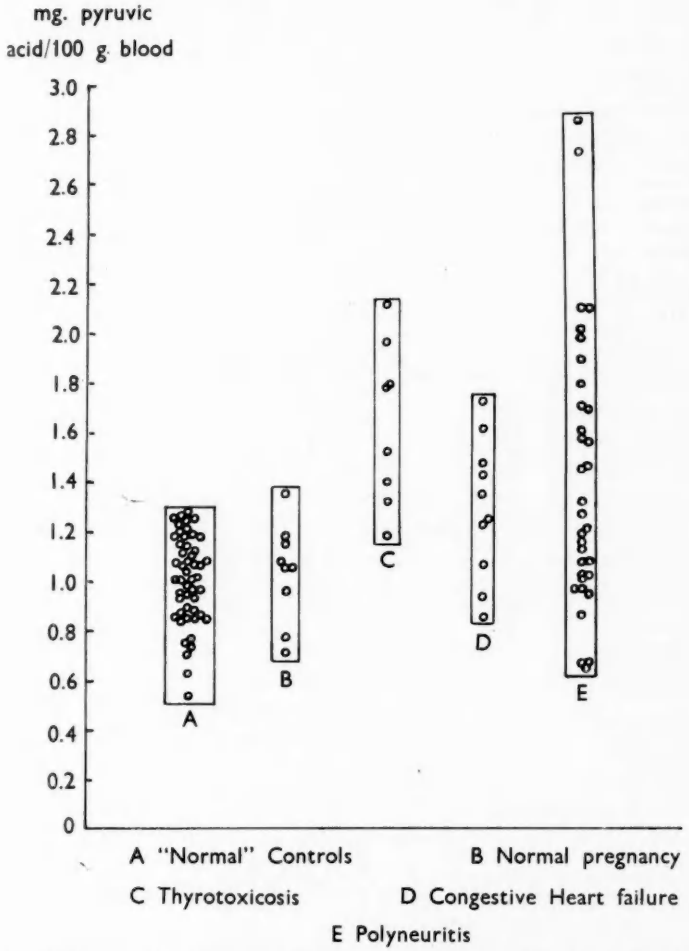


Fig. 1.—Maximum blood pyruvate values after administration of glucose in the cases studied.

The mean fasting value of the blood pyruvate level for the whole series is 0·76 mg. pyruvic acid/100 grammes blood; at 60 and 90 min. after the administration of the glucose the mean values are 0·92 and 0·94 respectively. The standard deviations for the 60 and 90 min. values are

TABLE I.—PYRUVATE METABOLISM TESTS IN NORMAL SUBJECTS AND IN HOSPITAL PATIENTS IN WHOM NO ABNORMALITY OF PYRUVATE METABOLISM WAS ANTICIPATED

(*Results expressed as mg. pyruvic acid/100 grammes blood at stated times after the administration of glucose*)

	0 *min.*	60 *min.*	90 *min.*
Healthy ambulant adult	0·67	0·75	0·85
Healthy ambulant adult	0·81	0·94	0·93
Healthy ambulant adult	0·81	—	0·84
Healthy ambulant adult	0·86	0·85	0·84
Healthy ambulant adult	0·99	1·00	0·86
Healthy ambulant adult	1·03	0·75	0·68
Healthy ambulant adult	0·57	0·96	0·55
Healthy ambulant adult	1·05	0·79	0·96
Healthy ambulant adult	0·45	0·53	0·49
Healthy ambulant adult	0·72	0·76	0·87
Healthy ambulant adult	0·83	0·86	0·98
Healthy ambulant adult	0·75	0·63	1·03
Dermatomyositis	0·92	1·00	—
Duodenal ulcer	0·83	0·89	0·54
Gastric ulcer	1·06	1·01	1·08
Microcytic anæmia	0·47	0·63	0·73
Duodenal ulcer	0·76	0·81	1·21
Lung abscess (convalescent)	0·58	0·63	0·88
Duodenal ulcer	0·54	0·97	1·24
Raynaud's syndrome	0·68	0·95	1·06
Pulmonary tuberculosis	0·42	1·10	1·14
Pulmonary tuberculosis	0·76	0·91	0·93
Duodenal ulcer	0·78	1·06	1·05
Cardiac asthma	0·83	1·10	1·19
Hæmatemesis (convalescent)	0·94	1·15	1·02
Hydrocele	0·78	1·09	1·10
Diabetic gangrene	0·57	0·95	0·96
Pulmonary tuberculosis	0·96	0·65	0·70
Anxiety neurosis	0·53	1·18	0·68
Toxic purpura	0·57	0·95	1·02
Disseminated sclerosis	0·73	1·25	1·08
Myopathy	0·52	1·01	1·20
Trigeminal neuralgia	0·68	1·14	1·26
Hemiplegia	0·61	1·11	0·82
Atypical facial neuralgia	0·85	0·96	1·00
Food poisoning (convalescent)	0·65	0·84	1·07
Disseminated sclerosis	0·68	0·80	0·85
Anxiety neurosis	0·53	1·18	0·68
Prolapsed intervertebral disc.	0·88	0·89	1·23
Prolapsed intervertebral disc.	0·90	1·12	0·98
Angioma of spinal cord	1·06	1·28	1·26
Epilepsy and hepatomegaly	0·97	1·06	1·18
Hepato-lenticular degeneration	0·70	0·62	0·57
Cirrhosis of liver	0·73	1·06	0·95
Tabes and meningo-vascular syphilis	0·87	0·81	0·84
Meningo-vascular syphilis	0·78	1·00	0·88
General paralysis of the insane	0·91	0·82	0·93
Tabes	0·50	0·77	0·76
Secondary syphilis	0·85	1·09	1·25
Gastric ulcer	0·72	0·68	1·08
Mean:	0·76	0·92	0·94
S.E.	±0·18	±0·17	±0·20

± 0·17 and ± 0·20, and therefore values above 1·26 and 1·34 mg. pyruvic acid/100 grammes blood (i.e. mean + 2 S.D.) may be said to be significantly raised above the normal range. The mean fasting level found for this series agrees well with the value of 0·79 mg./100 ml (range: 0·54–0·96) obtained in a series of 43 subjects by Friedemann, Haugen and Kmieciak (1945) and with the value of 0·76 ± 0·173 found by Klein (1942). The results for the 60 and 90 min. samples are also in good agreement with those obtained by Williams *et al* (1943), whose maximum normal values at these times did not exceed 1·4 mg./100 grammes.

As further controls, a group of 9 normal pregnant women, near to term, were included. Eight of these gave values well within the normal range (fig. 1), the ninth, a primipara delivered four days after carrying out the test, being just above the upper limit of normality. These observations confirm the findings of Svanteson (1946) who studied 12 women late in pregnancy using a similar pyruvate metabolism test.

Certain other conditions that might interfere with the application of this test to cases of polyneuritis have also been studied as preliminary controls. Himwich, Goldfarb and Cowgill (1932) and Cowgill and Palmieri (1933) have shown that the thiamine requirement is increased in thyrotoxic animals. In 7 out of 8 cases of thyrotoxicosis we have found raised pyruvate levels after the administration of glucose (fig. 1). Despite this, however, it cannot be concluded that thyrotoxic patients showing impaired pyruvate metabolism are necessarily deficient in thiamine, since it is possible that in such cases there may be an abnormal degree of loading of the tissues with glucose resulting from an abnormally rapid rate of absorption from the gut. In this connexion it is of interest to recall the demonstration by Barnes and King (1943) that thyrotoxic subjects may show impaired tolerance in the oral galactose tolerance test while showing a normal tolerance in the intravenous test, a finding which these workers interpreted as indicating an abnormally rapid absorption from the gut. In view of the report by Kato and Li (1941) of raised blood pyruvate values in rheumatic heart disease we have also carried out the test on 10 cases of congestive cardiac failure, and have found that high pyruvate levels after the administration of glucose may occur in the more severe cases (fig. 1).

Polyneuritis, Radiculitis and Myelopathy

The results on the 40 cases of polyneuritis, radiculitis and myelopathy are shown in Table II, the diagnoses being those of the physicians in charge.

The cases fall into two main groups: (1) 16 cases showing an abnormal rise of the blood pyruvate level after glucose administration, and (2) 24 cases showing no abnormality of blood pyruvate detectable by this test.

TABLE II.—RESULTS OF PYRUVATE METABOLISM TESTS AND OF DETERMINATIONS OF LACTATE PYRUVATE RATIO (L/P) IN CASES OF POLYNEURITIS, RADICULITIS AND MYELOPATHY (expressed as mg. pyruvic acid/100 grammes blood at times stated)

A. CASES OF POLYNEURITIS WITH IMPAIRED PYRUVATE METABOLISM

Case No.	Sex	Diagnosis	0 min.	60 min.	90 min.	L/P
1	F	Polyneuritis, probably thiamine deficiency	0·77	1·31	0·93	—
2	F	Chronic progressive peripheral neuritis	0·92	1·70	1·19	6·4
3	M	Chronic progressive peripheral neuritis	1·18	1·48	1·60	4·3
4	F	Polyarteritis nodosa, symmetrical polyneuritis	1·03	2·05	2·10	4·8
5	F	Nutritional myelopathy and peripheral neuritis	0·91	1·44	1·37	10·5
6	M	Carcinoma bronchi and polyneuritis	0·73	1·66	1·79	—
7	M	Acute infective polyneuritis (recovering)	1·06	1·22	1·45	—
8	F	Peripheral neuritis of unknown ætiology	1·25	1·97	1·62	6·1
9	M	Peripheral neuritis, partial gastrectomy sulphæmoglobinæmia	1·31	2·10	1·74	7·1
10	F	Peripheral neuritis of unknown ætiology	0·74	1·15	1·57	—
11	F	Peripheral neuritis and arteriosclerosis	—	1·55	1·34	—
12	M	Chronic peripheral neuritis	1·29	1·68	1·51	—
13	F	Polyneuritis with C.N.S. involvement	0·89	2·07	2·36	—
			1·05	2·29	2·86	—
14	F	Primary sensory neuropathy	2·08	2·73	2·03	7·1
			2·48	2·20	2·18	6·9
15	F	Motor polyneuritis	1·40	1·89	2·01	8·2
16	F	Peripheral neuritis and dementia	1·02	1·88	1·82	10·2

B. CASES OF POLYNEURITIS WITH NORMAL PYRUVATE METABOLISM

17	F	Pernicious anæmia, subacute combined degeneration and polyneuritis	0·77	1·05	1·18	—
18	F	Pernicious anæmia, subacute combined degeneration and polyneuritis	0·46	—	0·85	—
19	M	Pernicious anæmia, subacute combined degeneration and polyneuritis	0·55	0·96	0·88	—
20	F	Diabetic neuritis	0·82	0·62	0·66	8·1
21	F	Diabetic neuritis	0·97	0·63	0·66	7·5
22	F	Diabetic neuritis	—	1·07	1·07	—
23	M	Diabetic neuritis	0·49	0·64	0·63	9·4
24	M	Chronic progressive peripheral neuritis	0·65	0·89	1·02	—
25	M	Chronic progressive peripheral neuritis	0·74	0·94	0·72	—
26	M	Chronic progressive peripheral neuritis	0·71	1·20	1·01	—
			1·02	1·09	1·16	9·5
27	M	Polyneuritis	0·88	0·97	1·15	—
28	M	Polyneuritis and hepatomegaly	0·98	1·26	1·26	—
29	M	Polyneuritis, congestive cardiac failure	0·80	1·06	1·12	—
30	M	"Mononeuritis multiplex"	0·87	0·81	0·96	—
31	M	Methyl alcohol intoxication	0·53	1·07	0·75	10·4
32	M	Chronic ulcerative colitis and polyneuritis	0·48	1·00	0·87	9·0
33	M	Infective polyneuritis (recovering)	0·75	0·88	1·01	5·3
34	M	Infective polyneuritis (recovering)	0·84	0·88	0·91	8·1

C. CASES OF MYELOPATHY WITH NORMAL PYRUVATE METABOLISM

35	M	Myelopathy of unknown ætiology	0·90	0·97	1·19	—
36	F	Subacute combined degeneration	0·79	0·96	0·88	—
37	M	Myelopathy of unknown ætiology	1·05	1·10	1·15	—
38	M	Myelopathy of unknown ætiology	0·45	0·78	0·71	—
39	F	Subacute combined degeneration	0·91	—	1·03	—
40	F	Subacute combined degeneration	0·74	1·25	1·19	7·0

In Cases 13, 14 and 26, the results of two tests on each patient are given

The plan of the work has been to treat cases showing evidence of impaired pyruvate tolerance with massive intramuscular doses of thiamine; if, on repetition of the test after fourteen days of such therapy, it was still abnormal, the effect of treatment with BAL was next examined. In 2 of the 16 cases showing impaired tolerance it was not possible to assess the effects of either form of treatment. Case 7 was already recovering from an attack of acute infective polyneuritis, while Case 11 was discharged from hospital before further studies could be made. A third case, No. 12, had earlier received intensive treatment with thiamine without significant clinical improvement, and so was given BAL without further delay.

It will be noticed that the plan of the work and the grouping of the cases is based on their biochemical response to treatment. In general, some degree of clinical improvement has paralleled the biochemical response, but in no case has any dramatic clinical improvement resulted, nor could this be expected in a condition in which the possibility of recovery in the cord may have been irretrievably lost, and which, in the peripheral nerves, is dependent on the slow process of regeneration.

Effect of treatment with thiamine.—The remaining 13 cases with impaired pyruvate tolerance were given daily intramuscular injections of 100 mg. thiamine for two weeks. Six of them showed improvement in pyruvate metabolism, and their maximum blood pyruvate values at either 60 or 90 min., both before and after thiamine treatment, are given in Table III.

TABLE III.—MAXIMUM BLOOD PYRUVATE LEVELS IN CASES SHOWING IMPROVEMENT OF PYRUVATE METABOLISM FOLLOWING PARENTERAL THERAPY WITH THIAMINE

Case No.	*Diagnosis*	*Max. blood pyruvate value (mg. pyruvic acid/100 grammes blood at either 60 or 90 min.* *Before therapy*	*After thiamine*
1	Polyneuritis, probably thiamine deficiency	1·31	1·08
3	Chronic progressive peripheral neuritis	1·60	0·82
	Readmitted 4/12 later	1·68	0·88
5	Nutritional myelopathy and peripheral neuritis	1·44	0·98
	Readmitted 7/12 later	1·61	0·97
8	Peripheral neuritis of unknown ætiology	1·97	1·30
10	Peripheral neuritis of unknown ætiology	1·57	1·28
16	Peripheral neuritis and dementia	1·88	0·91

It will be seen that in 5 of these cases the highest value after treatment was within normal limits, and in the remaining case it was only slightly abnormal. None of the 40 cases of polyneuritis in this series gave a clear-cut story of a grossly deficient intake of thiamine, although in Cases

1, 8 and 16 it was probable that the intake was low. The possibility exists therefore that impaired absorption may in part have been responsible for the development of the neuritis, and in the following two cases described in detail, there was good evidence of deficient absorption of oral thiamine despite an adequate intake.

Case 3.—Three years before his admission in June 1949 Mr. G. B., aged 17, developed a large and painful ulcer beneath his left big toe, followed six months later by a similar but painless ulcer on the other foot. These ulcers healed slowly and tended to recur. One year before admission he noticed that his feet were numb, that he was walking clumsily with a stamping gait and that his ankles were becoming progressively weaker.

Bilateral cataracts were removed at the age of 7 but there was no history of cataract or nervous disease in any relative. His diet and living conditions had always been very good, he had not been exposed to any industrial hazard, and had not taken any patent medicines regularly.

Bilateral symmetrical loss of sensation to light touch of glove and stocking distribution extended in the arm to the elbow and in the leg to 6 in. below the inguinal ligament, and hypoalgesia to pin-prick was present below the mid-calves and wrists.

The anterior tibial, peroneal and calf muscles were wasted and very weak and there was slight weakness of the small muscles of the hand. All tendon reflexes were absent, the abdominals were present and the plantar responses flexor. The nerves were not abnormally thickened. The blood picture, urine and histamine test meal were normal. The C.S.F. was normal apart from a protein content of 70 mg. per cent. The W.R. was negative in the C.S.F. and blood. Porphyrinuria was not present. He was diagnosed as a case of chronic progressive peripheral neuritis.

He was treated with intramuscular injections of thiamine 100 mg. daily and Examen (liver extract) 2 ml. twice weekly, together with compressed yeast 15 grammes daily and Multivite tabs 2 t.d.s.

Before treatment a pyruvate metabolism test had shown impairment (max. value 1·59) but following treatment a normal curve was obtained. Clinical improvement was not evident.

On leaving hospital in August 1949 he continued to take thiamine by mouth until his readmission in November of that year. During this time, apart from gaining about 3 stones in weight, little significant improvement had taken place. Although he had been taking 25 mg. of thiamine and 15 grammes of yeast orally daily, a pyruvate metabolism test was found to be abnormal. Following intramuscular injections of 100 mg. of thiamine daily for two weeks, it returned to normal (max. 0·97 mg./100 ml.).

During his first admission in June 1949, the first two specimens of a test meal had not contained free acid; but following histamine acid phosphate a normal curve was obtained. On his second, and subsequently on a third admission, the test meal was repeated without histamine. On both occasions free acid was absent in all specimens, and the total acid was very low.

In December 1949 he was sent home for six months, and during this time had daily injections of thiamine mg. 100 intramuscularly. On his third admission, in June 1950, sensation was returning to his feet. He could appreciate pain and temperature, and postural sense had also improved. A pyruvate metabolism test at this time was normal (max. 1·28 mg./100 ml.).

It was felt at this time that there was evidence to suggest some impaired absorption of thiamine from the gut, and that possibly this was related to the achlorhydria which was present. He was therefore sent home for a further three months, and during this time he received acid hydrochlor. dil. (B.P.) 1 fluid drachm in a glass

of water a.c., and thiamine hydrochloride mg. 25 b.d. a.c. On readmission in August 1950, a pyruvate metabolism test was found to be normal (max. 1·03), and his clinical improvement maintained.

Case 5.—Miss J. T., aged 24, was healthy until four months before her first admission in March 1949, when she noticed a gradual onset of tingling in the feet associated with progressive numbness. Within three to four weeks the numbness had extended as high as her knees. At the same time she became ataxic and weak and within a month was walking only with the greatest difficulty. Her voice had been husky for one month. She had received three injections of Examen (liver extract) prior to admission without apparent improvement. She came of a family in which there was a strong history of pernicious anæmia. She had 8 sisters and 2 brothers; one brother and one sister had proved pernicious anæmia, the sister also showing neurological involvement. Another sister had an unexplained anæmia, two others suffered from ulcerated legs, and one other from ulcers in the mouth. She had always eaten a good mixed diet, worked in a silk factory and had not been exposed to any industrial hazard. She had not taken patent medicines and was almost a teetotaller.

Examination of her nervous system showed paralysis of the left vocal cord and marked weakness of the lower limbs. The ankle-jerks were absent, the knee-jerks obtained only on reinforcement and both plantar responses were extensor. Sensation was normal in the upper limbs, but in the legs hypoæsthesia extended above the ankles, hypoalgesia was present over the soles and dorsum of the feet, and vibration sense was absent in feet and shins. Postural sense was lost in the toes and impaired in the other joints of the legs, and there was gross ataxia on standing or attempting to walk. Her calves were abnormally tender on pressure. No abnormality was found in the cardiovascular, respiratory, renal or alimentary systems. The blood picture was normal apart from an eosinophilia presumed to be due to her recent injections of liver extract. Hb was 83 per cent (13·2 grammes), R.B.C. 4·2 million, C.I. 1·0, M.C.D. 7·2 μ. A sternal puncture was normal. There was a histamine-fast achlorhydria. Examination of urine and C.S.F. showed no abnormality. Porphyrinuria was not present, nor was there an excess of fat in the fæces. W.R. was negative in blood and C.S.F. X-ray examination of skull, chest and stomach showed no abnormality. A pyruvate metabolism test was found to be abnormal and she was given intramuscular thiamine 100 mg. daily for twenty-three days when the test was repeated and found to be normal. No other treatment was given apart from physiotherapy.

The improvement in the pyruvate metabolism test coincided with well marked clinical improvement shown by the recovery in function of her left vocal cord, by increased strength assessed by her ability to raise her extended leg from the bed, and by improvement in her ataxia. Dr. M. J. McArdle considered that the diagnosis of subacute combined degeneration of the spinal cord could not be excluded, but preferred that of nutritional myelopathy with a peripheral neuritis in view of her age, normal blood count and because of the paralysed vocal cord which is rare in subacute combined degeneration but not uncommon in advanced thiamine deficiency (Spillane, 1949).

From 25.4.49 she was treated with Examen 2 c.c. intramuscularly thrice weekly, thiamine 50 mg. b.d. and nicotinamide 200 mg. t.d.s. each by mouth. She continued to improve and was discharged on 19.6.49. She then received intramuscular injections of liver from her own doctor, until September 1949. After this she received no treatment until November 1949.

She was readmitted on 23.11.49, having had no treatment for two months. Her improvement had been maintained; she still complained of numbness of her feet and of pins and needles, but she could now walk unaided for up to 2 miles; her upper limbs and voice were normal. On examination there was still moderate weakness of the right leg with bilateral extensor plantar responses. Sensation was

now impaired only in the soles of her feet and vibration sense was markedly impaired at and below the ankles. Her blood picture was still normal and gastric analysis again showed a histamine-fast achlorhydria. A pyruvate metabolism test was found to be abnormal. Following a course of thiamine 100 mg. intramuscularly daily for two weeks the test was repeated and found normal. She was discharged in December 1949, and from then until July 1950 she received thiamine mg. 100 intramuscularly twice weekly and thiamine mg. 25 daily by mouth. No liver injections were given between these dates.

She was admitted again in July 1950, when her neurological condition was found to be improved. She had no paræsthesiæ in the legs, and the soles of her feet did not seem to her to be so numb. On examination, knee and ankle power was found to be normal, and only slight weakness of dorsiflexion of the toes was present. The knee-jerks were brisk, and the ankle-jerks, although weak, were present. The plantar responses were bilaterally extensor. Her sensory changes were much the same as in November 1949.

A blood picture, after eleven months without liver injections, was quite normal, and was taken to exclude the possibility of pernicious anæmia. A pyruvate metabolism test was normal (max. 1·27 mg./100 ml. blood).

In both these cases a peripheral neuritis with or without involvement of the cord developed whilst on an adequate diet. Both responded rapidly to intramuscular thiamine although improvement was initially more definite biochemically than it was clinically. Both suffered a biochemical relapse despite oral thiamine therapy when intramuscular injections of this compound were discontinued, followed by recovery when it was resumed (the second patient had not received oral thiamine therapy for two months before her second admission to hospital but she was eating a very adequate diet).

Among other possibilities, defective absorption or abnormal destruction of the vitamin in the gut would seem to be the most likely explanation for this anomalous behaviour. It is noteworthy that in these 2 patients and also in Case 16, gastric analysis showed absence of free HCl.

Case 16.—Mr. J. W., aged 74, had been on a diet only moderately deficient in the vitamin B complex, although his intake of carbohydrate had been high. He had had nocturnal mental confusion, anorexia, paræsthesia in the thighs and cramps, increasing weakness and unsteadiness in the legs for about a year. The main features on examination were the mental confusion, a dry fissured magenta tongue, well-marked angular stomatitis, sluggish knee reflexes, an absent right ankle-jerk, and hyperalgesia over the antero-lateral aspect of both thighs. A test meal showed a hypochlorhydria, and a pyruvate metabolism test was abnormal (max. value 1·88 mg./100 ml.). This was restored to normal by a course of injections of thiamine, and his appetite, weakness and ataxia improved at the same time. The lesions in the mouth, however, did not respond to injections of riboflavin, nicotinic acid or pyridoxine. On discharge his mental state was improved and the paræsthesiæ and cramps in his legs had not recurred.

In two other cases (Nos. 1 and 10) of chronic progressive polyneuritis, the pyruvate metabolism returned to within normal limits following intramuscular thiamine, but in only one (Case 1) was the diet deficient in this substance. In both cases treatment with thiamine was followed by considerable, though slow, clinical improvement. Case 8 is tentatively

included as having responded to thiamine, for although the second pyruvate metabolism test was just abnormal following intramuscular thiamine, a significant improvement had nevertheless occurred. At the time it was thought that she was not responding satisfactorily to thiamine, and she was then given a course of BAL, although the daily thiamine injections were continued. A third pyruvate metabolism test again showed very slight impairment of function. She left hospital at this point and it has not been possible to trace her subsequent progress. She had been taking a deficient diet for three years, and eight years before had had an earlier attack of peripheral neuritis which had cleared up completely following treatment with thiamine.

Some degree of clinical benefit following treatment with thiamine occurred in a seventh case (Case 9, not included in Table III) without any clear-cut evidence of improvement in pyruvate metabolism.

Case 9.—Mr. J. P., aged 57. Paræsthesiæ had begun seven months before admission, and two months after a partial gastrectomy for a gastrojejunal ulcer. He was found in addition to have sulphæmoglobinæmia due to phenacetin and as a further complication an X-ray showed him to have infiltration at the apex of the left lung. His sedimentation rate (Westergren) was 49 mm. in one hour, but no tubercle bacilli were found in his sputum. Although the paræsthesiæ improved following intramuscular thiamine, the pyruvate values at 60 and 90 min. (1·71 and 1·61 mg.%) showed only a slight improvement. The fasting value, however, which initially had been raised, returned to normal (1·31 to 0·9 mg.%). It is possible that the failure of the pyruvate metabolism test to mirror the subjective clinical improvement may have been due to unusually rapid absorption of the glucose following an abnormally rapid emptying from the remnant of his stomach (he had symptoms very suggestive of the dumping syndrome). Because of the clinical improvement, this patient was discharged on thiamine without receiving BAL.

Effect of treatment with BAL.—The remaining 6 cases of the group of 13 treated parenterally with thiamine failed to show any response either biochemically or clinically. A course of injections of BAL was therefore next given according to the scheme laid out in the report from the Medical Research Council (1947), except that 4 ml. of 5 per cent BAL was given at each injection instead of 2 ml. as recommended. The pyruvate metabolism test was repeated as soon as the course was completed. Case 12, mentioned earlier as having received intensive oral thiamine therapy before admission to hospital, was also given BAL after a test had revealed impaired pyruvate tolerance.

Table IV shows the blood pyruvate levels in the 3 cases which showed, biochemically, an improvement following BAL.

In 2 of the cases (Nos. 6 and 12) a return to normal of the pyruvate metabolism test following BAL therapy coincided with clinical improvement; in the third case (No. 4), clinical and biochemical improvement followed BAL but was not thought to be due to it.

TABLE IV.—MAXIMUM BLOOD PYRUVATE LEVELS IN CASES REFRACTORY TO THIAMINE THERAPY BUT SHOWING IMPROVEMENT OF PYRUVATE METABOLISM FOLLOWING TREATMENT WITH BAL

Case No.	*Diagnosis*	*Max. blood pyruvate value (mg. pyruvic acid/100 grammes blood) at either 60 or 90 min.*			
		Before therapy	*After Thiamine*	*After 1st course BAL*	*After 2nd course BAL*
4	Polyarteritis nodosa, symmetrical polyneuritis	2·10	1·89	1·38	0·82
6	Carcinoma bronchi and polyneuritis	1·79	1·92	1·61	1·21
12	Chronic peripheral neuritis	1·68	—	1·16	1·29

In 2 of these cases that appeared to respond to BAL there was a history of previous exposure to heavy metals, but in one of them other forms of treatment were given concurrently and no claims as to the effects of BAL in this case can be made.

Case 6.—Mr. G. M., aged 55. Apart from low back pains which he had not experienced for four years, Mr. G. M. had been in good health until sixteen months before his admission to hospital. He then noticed a feeling as though a bandage were wrapped around the lower part of his chest, and began to suffer from aching pains from the buttocks to the heels. Two months later his walking became very unsteady, and for nine months his hands and arms had been very clumsy. For ten months he had not been free from severe pain in the back of the neck extending from the base of the skull down the middle of the neck and across the shoulders. Unpleasant feelings as though he were "sitting on red-hot cinders" and "as though his legs were wrapped in wire wool" had been present for three months. Difficulty in micturition had been present for two months. He had lost weight rapidly and had become dyspnœic on exertion, but had had no cough, hæmoptysis or pain in the chest. For about twenty years until 1934 he was employed as a brazier and welder and used a number of metal-containing fluxes some of which he believes contained lead.

On examination it was noted that there was general muscle wasting and hypotonia. Power was good and posture well maintained but there was slight incoordination of all movements. All tendon reflexes were absent in the arms and legs, the plantar responses were both extensor, the abdominal reflexes present and equal. Joint sense and vibration sense were impaired in the lower limbs, and there was a qualitative change in sensation in his hands and feet. Cranial nerves were normal. Movement of the right side of the chest was diminished, but no other abnormality was detected. Fractional test meal, blood picture, urine and C.S.F. were normal. The W.R. was negative in the blood and C.S.F., and the erythrocyte sedimentation rate (Westergren) was 21 mm./1 hr. X-ray of the chest showed a carcinoma of the right upper lobe bronchus. Sir Charles Symonds diagnosed spinal cord and peripheral nerve degeneration of the type associated with pernicious anæmia but seen sometimes in association with carcinoma of the stomach or, as in this case, with carcinoma of the bronchus.

He was given a series of exposures to deep X-rays between October and December 1949 with excellent results. A pyruvate metabolism test was first performed on 13.10.49 and proved to be abnormal. He was therefore treated with 100 mg. thiamine daily by intramuscular injection until 5.12.49 when a further test was found to be still abnormal, although he had by then begun to benefit from the deep X-ray therapy. A course of BAL totalling 44 ml. by intramuscular injection was given commencing on 7.12.49 and ending on 12.12.49. As a further test showed an improved but still abnormal result, a second similar course of BAL

was given and a further test made on 1.2.50 when normal values were obtained. Despite two further courses of BAL no further clinical improvement occurred during the following three months. The upper lobe collapse was no longer visible on X-ray.

Case 12.—Mr. H. S., aged 65, enjoyed good health until four years before admission when he first noticed that his feet were numb and that he had painful tingling in the toes. These symptoms became progressively worse and for three months had also been present in his hands. He had had difficulty in walking, especially in darkness, for three years and had been forced to use a stick.

There was no relevant family history of previous illness. He had always eaten a good mixed diet, and drank and smoked moderately. Since 1932 he had been engaged in the manufacture of fireworks and other articles necessitating the handling of lead azide, mercury fulminate, and many chemical mixtures of unknown composition. No other person employed with him, so far, as he was aware, had suffered from any complaint similar to his own.

On examination, there was weakness and wasting of the muscles of the lower limbs, most pronounced distally, with extreme weakness of dorsiflexion of the foot, worse on the right, together with loss of all forms of sensation extending to the knee on the right side and slightly lower on the left. The knee and ankle tendon reflexes were absent and the plantar responses flexor. Some decreased perception of temperature was found in the finger tips. His gait was ataxic, and his calf muscles extremely tender. He had a mild leucoplakia of the tongue and a moderate degree of emphysema. B.P. 190/100.

Certain investigations had been made during the three years prior to his admission in January 1950. Blood picture and gastric analysis were normal. The C.S.F. contained 100 mg. protein/100 ml., but was otherwise normal. The W.R. was negative in the C.S.F. and the blood, and no abnormality was found in the urine. A glucose tolerance test was normal. During this time he had received prolonged and intensive treatment with thiamine without significant clinical improvement.

A pyruvate metabolism test performed on 15.1.50 showed impaired tolerance. A course of BAL was given and a second test then showed a normal response. At this time, too, it was noted that his calf muscles were no longer tender. No objective change in his condition could be demonstrated.

Because a further pyruvate metabolism test a fortnight later tended to the upper limit of normality he was given a second course of BAL. Unfortunately, an unsuccessful attempt at nerve biopsy was made just before the commencement of the second course; the wound became infected, and he was then intermittently pyrexial until March 17, 1950. Because of this, a pyruvate metabolism test was not made until he had been apyrexial for three days. The test showed values in the upper range of normality, but since it was performed eighteen days after the end of the second course of BAL, it hardly provided a true indication of its effect.

Case 4.—Mrs. K. S., aged 40. This case of periarteritis nodosa with symmetrical peripheral neuritis involving all her limbs had not shown any significant improvement after a course of injections of thiamine. She was given two courses of BAL but it was not possible to repeat the test until two months later, when it was only slightly abnormal. When repeated after a further two months the pyruvate did not rise above 0·82 mg. During this time she had been making a slow though chequered recovery, which was not thought to be in any way related to the BAL.

Cases showing no improvement with either thiamine or BAL.—In the remaining 4 cases that were treated with BAL after an unsuccessful period of thiamine therapy, both pyruvate metabolism and the clinical condition

remain unchanged (Table 5). They were all severely and chronically affected, but in other respects did not differ from cases responding to therapy. There was no special incidence of either sensory or motor nerve or cord involvement. The disease was confined almost entirely to the sensory nerves in Case 14, to the motor nerves in Case 15, whereas in Cases 2 and 13 both motor and sensory nerves were involved. Their ages varied widely, but it should perhaps be noted that they were all females.

TABLE V.—MAXIMUM BLOOD PYRUVATE LEVELS IN CASES FAILING TO SHOW IMPROVEMENT AFTER THERAPY WITH EITHER THIAMINE OR BAL

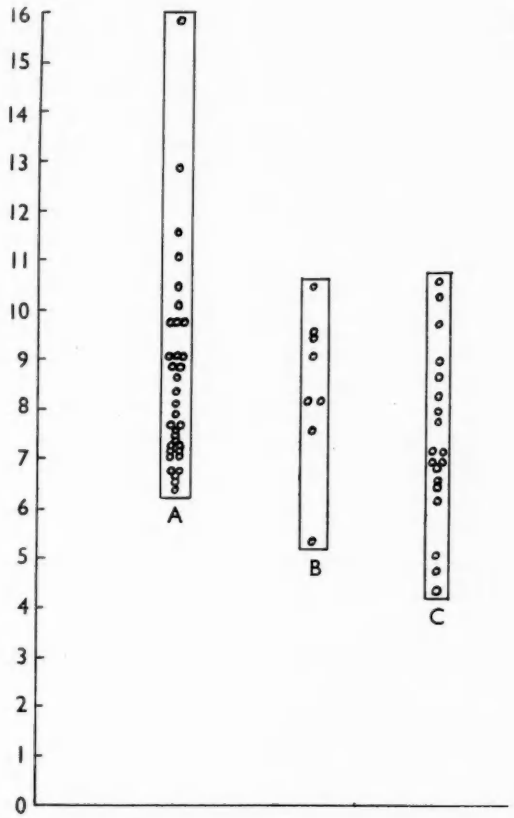
Case No.	*Diagnosis*	*Max. blood pyruvate value (mg. pyruvic acid/100 grammes blood) at either 60 or 90 min.*		
		Before therapy	*After thiamine*	*After BAL*
2	Chronic progressive peripheral neuritis	1·70	1·34	1·64
13	Polyneuritis with C.N.S. involvement	2·36 2·86	2·00	2·23
14	Primary sensory neuropathy	2·73 2·20	2·40	2·12
15	Motor polyneuritis	2·01	1·86	2·65

In Cases 13 and 14 the results of two tests on each patient are given before therapy.

Cases showing no detectable abnormality of pyruvate metabolism.—Of the 24 cases giving a normal response to the pyruvate metabolism test, 18 were cases of peripheral neuritis with or without evidence of cord involvement; in 4 of these the neuritis occurred in elderly and inadequately treated diabetics, and in another three cases it was associated with subacute combined degeneration of the cord. The remaining 11 cases had nothing characteristic to distinguish them from those showing abnormal pyruvate tolerance although it may be of significance that they were all males. Case 27 had had intensive oral thiamine therapy for some months prior to admission though without clinical benefit. Case 34 was already recovering from an attack of acute infective motor polyneuritis, and had also received intensive therapy with thiamine and other vitamins.

Finally, 6 cases of myelopathy without demonstrable peripheral neuritis have also been examined. Three have been instances of subacute combined degeneration of the cord and, like those having peripheral neuritis, no abnormality of pyruvate metabolism was found. The remaining 3 cases in which the ætiology of the condition was not known also showed normal pyruvate metabolism.

The lactate-pyruvate ratio.—The suggestion of Stotz and Bessey (1942) and of Goldsmith (1948) that the lactate-pyruvate ratio (L/P) is lowered in thiamine deficiency, was not found of value in identifying cases in whom there was reason to suspect thiamine deficiency, or in whom



A "Normal" Controls
B Polyneuritis with normal pyruvate metabolism
C Polyneuritis with impaired pyruvate metabolism

FIG. 2.—Fasting blood lactate-pyruvate ratios.

pyruvate metabolism was impaired from other causes. The L/P ratio was first studied in 34 blood samples from 5 normal adult subjects and 16 patients in whom there was no reason to suspect any disturbance of lactate or pyruvate metabolism. Blood samples taken after the ingestion of glucose have not been included. It can be seen from fig. 2 that the lowest L/P ratio in this series was 6·3, the mean being 8·6. The ratio was determined in 5 of the cases responding biochemically to thiamine and in only 2 was the ratio below the lower limit of normal.

Fifteen blood lactate estimations were also carried out on 6 cases of polyneuritis with impaired pyruvate metabolism refractory to thiamine.

Although the mean fasting L/P ratio of 7·2 was low, on only two occasions was the initial L/P ratio below 6·3. Similarly after glucose, the L/P ratio was below 6·3 in only 3 out of 36 blood samples from 9 cases with impaired pyruvate metabolism.

The L/P ratio was found normal both before and after the ingestion of glucose in 8 of 9 cases of polyneuritis or myelopathy having normal pyruvate tolerance. The exception was Case 33 recovering from acute infective polyneuritis who at 0 min., 60 min. and 90 min. gave L/P values of 5·3, 6·2 and 6·9.

It is concluded, therefore, that the determination of the L/P ratio is of little value as a diagnostic measure. Its sole possible value would appear to lie in the interpretation of a raised blood pyruvate where there was reason to suppose that anoxæmia from exercise, heart failure or prolonged stasis might have given rise to a high value. In such circumstances a low L/P ratio would suggest that the high pyruvate was due to impairment of pyruvate metabolism by some cause other than anoxæmia.

Discussion

The results obtained in this unselected series of patients with peripheral neuropathy indicate that the administration of a loading dose of glucose can reveal an impairment of pyruvate metabolism in certain cases even though the fasting blood pyruvate level may be within normal limits. As far as we are aware, no attempt has yet been made to measure blood pyruvate levels after a loading dose of glucose in a series of cases of peripheral neuritis not obviously associated with a dietary deficiency of thiamine. The cases investigated by Williams *et al.* (1943) were subjects with induced thiamine deficiency; Stolte and Engel (1948) used a similar pyruvate metabolism test on patients with clinical symptoms of beriberi in the Dutch East Indies.

From the biochemical point of view it would seem that the 40 cases of polyneuritis studied by us fall into three groups:

(1) Cases in which no abnormality of pyruvate metabolism was detected.

(2) Cases which before treatment showed a significant impairment of pyruvate metabolism, but in which the blood pyruvate levels after glucose administration fell to normal following intramuscular therapy with thiamine.

(3) Cases showing impaired pyruvate metabolism, in whom this biochemical disturbance was unaffected by massive intramuscular thiamine therapy.

Despite the claim made by Furmanski (1948) we feel that the 3 cases studied by us, in whom treatment with BAL was followed by a return

of pyruvate tolerance to normal, do not justify us in stating that we have clear evidence of the existence of a fourth type—a type showing impaired pyruvate tolerance, unaffected by treatment with thiamine, but restored, biochemically, to normal by BAL. It is unfortunate that the clinical responses of 2 of these cases should have been confused by other complicating factors. However, it is worth noting that both these cases gave a history of occupational exposure to hazards of heavy metal intoxication, and in view of our present knowledge concerning the biochemical disturbances accompanying metal intoxications and their clinical response to BAL, it seems very likely that there does exist a fourth type of polyneuritis, responding to treatment with BAL both clinically and biochemically. It should perhaps be pointed out that we have not had opportunity of studying, in the acute phase, the blood pyruvate levels in those cases of polyneuritis which recover spontaneously.

In this series there does not appear to be any correlation between the clinical diagnosis and the biochemical type, as defined above, with the exception of the cases with impaired tolerance thought to be due to thiamine deficiency, and the 4 cases of diabetic neuritis and 6 cases of subacute combined degeneration of the cord, all of whom showed normal pyruvate tolerance. In this latter connexion it is interesting to note that Goodhart and Sinclair (1940) found a normal level of blood co-carboxylase in subacute combined degeneration; further in 5 patients with diabetic neuritis they found a low blood co-carboxylase level in only one, this patient also being an alcohol addict. A demonstrable defect in pyruvate metabolism does not necessarily depend on the severity of the condition since we have carried out tests, all of which were normal, on patients with polyneuritis of varying degrees of severity. On the other hand, in patients in whom a metabolic defect has been shown, some correlation, as might be expected, does appear to exist between the severity of the condition and the degree of metabolic impairment.

As pointed out earlier, it is now known that a variety of factors other than an inadequate dietary intake of thiamine can influence pyruvate metabolism, and it is not surprising therefore that only a proportion of cases with impaired tolerance have shown a return to normal of their blood pyruvate levels on treatment with parenteral thiamine. 3 of these cases (Nos. 3, 5, and 16) were associated with a hypochlorhydria or achlorhydria, a finding which may be of significance in connexion with the demonstration that decreased acidity of the gastro-intestinal tract favours greater destruction of thiamine (Sinclair, 1939; Goodhart and Sinclair, 1940; Melnick, Robinson and Field, 1941; Melnick and Oser, 1947). Thus, in Cases 3 and 5 treatment with intramuscular thiamine caused a return to normal of pyruvate metabolism whereas oral administration of this vitamin was ineffective; in Case 3, however, a normal

pyruvate tolerance test was obtained after a further period of three months during which oral thiamine together with hydrochloric acid was given daily. Unfortunately, our clinical material did not include any clear-cut and indisputable case of thiamine deficiency of nutritional origin, and although a considerable but slow improvement following therapy was observed in the 6 cases mentioned in Table III, in no case was the response dramatic. But in view of the chronicity of many cases of peripheral neuritis, and on account of the nature of the neuronal lesion involved, it is to be expected that even though a metabolic lesion can be rapidly rectified by thiamine therapy, the anatomical repair and therefore the clinical response will in many cases be slow and possibly incomplete. It is suggested therefore that a pyruvate metabolism test carried out shortly after a course of intensive parenteral thiamine therapy may give a more rapid indication of the value of such therapy than would be available by basing conclusions solely on clinical criteria. A further use of this test is in providing an indication as to those cases that may be regarded as unlikely to benefit from thiamine therapy since if a normal pyruvate tolerance is obtained after glucose administration, it seems unlikely that a thiamine deficiency is the major cause of the condition.

The cause of the raised blood pyruvate levels in the group which responded neither to thiamine nor to BAL is obscure. It may be that in some of these cases the lesion is caused by the presence of some "anti-thiamine" substance, similar to that described in connexion with the Chastek paralysis of captive foxes (Green, Carlson and Evans, 1941; Krampitz and Woolley, 1944), or present in extracts of bracken (Weswig, Freed and Haag, 1946; Thomas and Walker, 1949). It was with this possibility in view that we chose massive doses of 100 mg. thiamine daily by intramuscular injection in attempting treatment. We have of course no direct evidence that the biochemical defect in this latter group is playing any causative role in the neuropathy, although by analogy with the lesion in pyruvate metabolism which accompanies thiamine deficiency, it might be anticipated that it is a reflection of some related underlying biochemical defect. This is more probable, since this group of patients has, on the whole, shown the most severe impairment of pyruvate metabolism.

Only 5 of the 16 cases showing impairment have had raised fasting blood pyruvate levels, and it has been shown that the determination of the lactate-pyruvate ratio has not provided any better evidence. It may be concluded that the clearest evidence of an abnormality of pyruvate metabolism is obtained by the use of a pyruvate metabolism test after a loading dose of glucose.

SUMMARY

(1) A study has been made of the blood pyruvate levels after a loading dose of glucose, and of determinations of the lactate-pyruvate ratio, in an unselected series of 40 cases of peripheral neuritis and myelopathy.

(2) It has been shown that biochemically these cases appear to fall into at least three types,

(i) cases showing no defect of pyruvate metabolism,

(ii) cases showing impairment of pyruvate metabolism, rectifiable by therapy with thiamine,

(iii) cases showing impairment of pyruvate metabolism unaffected by massive intramuscular thiamine therapy.

(3) The effect of treatment with BAL on thiamine-resistant cases was studied; the possibility of a type of lesion in certain cases of polyneuritis amenable to treatment with this drug is discussed.

(4) Impairment of pyruvate metabolism can be demonstrated more clearly by a pyruvate metabolism test than by determination of a fasting value or of the lactate-pyruvate ratio.

(5) The clinical aspects of the cases and their response to therapy with thiamine and BAL are discussed in relation to the biochemical findings.

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REFERENCES

BARKER, S. B., and SUMMERSON, W. H. (1941) *J. biol. Chem.*, **138**, 535.
BARNES, C. G., and KING, E. J. (1943) *Quart. J. Med.*, **12**, 129.
BUEDING, E., STEIN, M. H., and WORTIS, H. (1941) *J. biol. Chem.*, **140**, 697.
——, WORTIS, H., and STERN, M. (1942) *J. Clin. Invest.*, **21**, 85.
COWGILL, G. R., and PALMIERI, M. L. (1933) *Amer. J. Physiol.*, **105**, 146.
ELSOM, K. O., LUKENS, F. D. W., MONTGOMERY, E. H., and JONAS, L. (1940) *J. Clin. Invest.*, **19**, 153.
FRIEDEMANN, T. E., and HAUGEN, G. E. (1943) *J. biol. Chem.*, **147**, 415.
——, ——, and KMIECIAK, T. C. (1945) *J. biol. Chem.*, **157**, 673.
FURMANSKI, A. R. (1948) *Arch. Neur. Psych.*, **60**, 270.
GOLDSMITH, G. A. (1948) *Amer. J. Med. Sci.*, **215**, 182.
GOODHART, R., and SINCLAIR, H. M. (1940) *J. biol. Chem.*, **132**, 11.
GREEN, R. G., CARLSON, W. E., and EVANS, C. A. (1941) *J. Nutr.*, **21**, 243.
HIMWICH, H. E., GOLDFARB, W., and COWGILL, G. R. (1932) *Amer. J. Physiol.*, **99**, 689.

JOINER, C. L., THOMPSON, R. H. S., and WATSON, D. (1950) *Guy's Hosp. Rep.*, **99**, 62.
KATO, K., and LI, P. J. (1941) *Amer. J. Dis. Child.*, **61**, 1222.
KEYS, A., HENSCHEL, A., TAYLOR, H. L., MICKELSEN, O., and BROZEK, J. (1945) *Amer. J. Physiol.*, **144**, 5.
KLEIN, D. (1942) *J. biol. Chem.*, **145**, 35.
KRAMPITZ, L. O., and WOOLLEY, D. W. (1944) *J. biol. Chem.*, **152**, 9.
MELNICK, D., and OSER, B. L. (1947) *Vitamins and Hormones*, **5**, 39.
——, ROBINSON, W. D., and FIELD, H. (1941) *J. biol. Chem.*, **138**, 49.
M.R.C. Report from the BAL Conference (1947) *Lancet* (ii) 497.
PETERS, R. A. (1936) *Lancet* (i), 1161.
——, SINCLAIR, H. M., and THOMPSON, R. H. S. (1946) *Biochem. J.*, **40**, 516.
——, STOCKEN, L. A., and THOMPSON, R. H. S. (1945) *Nature, Lond.*, **158**, 616.
——, and THOMPSON, R. H. S. (1934) *Biochem. J.*, **28**, 916.
PLATT, B. S., and LU, G. D. (1939) *Biochem. J.*, **33**, 1525.
ROSS, R., and REYNOLDS, E. S. (1901) *Brit. Med. J.*, (ii) 979.
SARKAR, S. N. (1948) *Nature, Lond.*, **162**, 265.
SEXTON, G. B., and GOWDEY, C. W. (1947) *Arch. Derm. Syph.*, **56**, 634.
SINCLAIR, H. M. (1939) *Proc. Roy. Soc. Med.*, **32**, 812.
SPILLANE, J. D. (1949) Nutritional Disorders of the Nervous System. Edinburgh. (E. & S. Livingstone Ltd.)
STOLTE, J. B., and ENGEL, C. (1948) *Internat. Z. Vitaminforsch.*, **19**, 336.
STOTZ, E., and BESSEY, O. A. (1942) *J. biol. Chem.*, **143**, 625.
SVANTESON, G. (1946) *Acta. Obst. Gyn. Scand.*, **26**, 41.
THOMAS, B., and WALKER, H. F. (1949) *J. Soc. Chem. Ind.*, **68**, 6.
THOMPSON, R. H. S., and JOHNSON, R. E. (1935) *Biochem. J.*, **29**, 694.
——, and WHITTAKER, V. P. (1947) *Biochem. J.*, **41**, 342.
WESWIG, P. H., FREED, A. M., and HAAG, J. R. (1946) *J. biol. Chem.*, **165**, 737.
WILLIAMS, R. D., MASON, H. L., POWER, M. H., and WILDER, R. M. (1943) *Arch. Int. Med.*, **71**, 38.
WILSON, H. E. C., and GHOSH, B. K. (1937) *Ind. Med. Gaz.*, **72**, 147.

FITS OF LAUGHTER (SHAM MIRTH) IN ORGANIC CEREBRAL DISEASE

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Cerebral Mechanism for Laughter

There must be a "centre" for laughing, if only to co-ordinate the movements involved in the act. When we laugh the whole musculature of the face is first strongly innervated, then the muscles of the throat and jaw, then the diaphragm acts rhythmically, and with it the muscles of the chest, abdomen, neck and back, and to a less degree those of the limbs. The activities of the facial nuclei, the motor nuclei of the trigeminal nerve, the nucleus ambiguus of each side of the medulla, the respiratory centres, and the motor cells for the muscles of the neck and other parts have therefore to be stimulated and co-ordinated into one harmonious activity. The mechanism by which this is brought about is very imperfectly known, but, as a result of clinical observation certain facts are established and other points are surmised. It is known, for instance, that the stimuli for emotional movement are not transmitted to the medullary and spinal centres by way of the pyramidal tract; in most cases of hemiplegia in which the pyramidal tract is interfered with at the internal capsule or higher, emotional movement of the face and other parts is not paralysed, but is, in fact, somewhat greater on the paralysed than on the sound side as the result of the withdrawal of a "pyramidal" control. Even with severe bilateral cortical (or hemisphere) disease the function of laughing usually remains intact and it is evident that the mechanism on which it depends is subcortical. It was formerly considered that the centres concerned lay in the thalamus (Brissaud, 1895) but since the work of Bard (1928) who showed that the exhibition of "sham rage" in cats was dependent on the posterior part of the hypothalamus, there has been a general assumption that centres for the various kinds of emotional expression exist in that part of the brain in man also. The fibre-pathway to the lower centres concerned has not been identified, but Kinnier Wilson (1924) (writing before Bard's discovery) brought forward clinical evidence that it passed close to the anterior and inferior surface of the thalamus, and that the fibres concerned with emotional movement of the face decussated in the upper part of the mid-brain and passed down in the tegmentum, well behind

the pyramidal tract in the crus: in one of his cases a lesion below that level and confined to the tegmentum caused paralysis of emotional movement of the face on the same side as the lesion.

Disorders of Laughter

Under normal healthy conditions the "laughter centre," wherever situated, is excited in association with the occurrence of the appropriate emotion, and the outward manifestation produced—the laughter—if not inhibited—corresponds in time and in degree to the emotion felt, but in organic cerebral disease various disorders of the laughing function are encountered.

Paralysis of laughter, in the sense of paralysis of the central mechanism, is a condition I have never observed, but Dott (1938) mentions a case of hypophyseal cyst in which the physical ability to laugh or to weep was absent, though the corresponding emotions were present.

There are several different groups of circumstances in which laughter may be excessive. In the first place the emotion may be excessive and excessive laughing may occur in consequence. In such cases the excessive laughter is, of course, genuine. The most remarkable case of this kind I have ever encountered was that of a woman of about 50 years of age who had a meningeal tumour of the size of a golf ball arising from the nasal groove and situated therefore between the lower parts of her frontal lobes. This patient in the previous two years had developed a remarkable hilarity; she made jokes about everything and could not restrain her laughter. To examine her in the ward was an embarrassing adventure because she made jokes about different parts of the examination and kept the ward in fits of laughter. Her laughter was obviously backed by appropriate emotion and was infectious and a pleasure to see and hear.

Much more frequently excessive laughing (and crying) in cases of organic cerebral disease occurs as a consequence of impairment of a controlling mechanism, so that laughing once excited, becomes excessive in degree and continues possibly long after the patient desires it to stop. In such cases the stimulus which initiates the laughter is ordinarily a psychological one and appropriate in quality, though possibly one that would ordinarily be inadequate. Such laughter occurs in various conditions in which the function of both pyramidal tracts is impaired; it is met with not infrequently in cases of pseudo-bulbar palsy and sometimes in other cases of generalized cerebral arterio-sclerosis; it occurs also in amyotrophic lateral sclerosis and in certain cases of disseminated sclerosis; apart from these last, the patients concerned are mostly middle-aged or elderly subjects.

Thirdly, the laughing centre may be excited by the irregular dis-

charges of epilepsy so that in rare instances laughter occurs as part of an epileptic fit or as an epileptic equivalent. The knowledge of such cases has been well summarized by Marchand and de Ajuriaguerra (1948) in their recent book, Les Epilepsies. The laughing occurs without any recognizable exciting cause; in general the patients are unaware of it and have no recollection of it afterwards. What occurs is an appearance of laughter, a caricature of a laugh, the external manifestation of laughing without the appropriate emotional or affective accompaniment. In a considerable proportion of cases the laughter is not "hearty" but merely a giggle. It should be pointed out that some of these cases have very peculiar features and in particular that in a number of them the attacks of laughing are accompanied by "orgasmolepsy" (Rothfield, Wilder, Lopen-Aydallo and Sempan), a fact which lends support to the suggestion that the motor centres for laughter and for certain sexual motor activity may be neighbours.

The cases that I am concerned with here are of a slightly different character from the idiopathic epileptic cases, being cases of organic cerebral disease. These cases suggest that, again in rare instances, fits of laughter may occur in association with organic lesions which, so to speak, "irritate" the centre. If so, the episodes are comparable to Jacksonian (motor or sensory) fits.

Cases

Before the War I had seen two of the cases described below (2 and 3), and Dr. Astley Clarke of Leicester had most generously sent me full details of a case that I had heard him refer to at the British Medical Association in 1931 (Case 1). Unfortunately all the records of these cases have been lost so the accounts of them here are given from memory and are not as complete as I would like them to be. Case 4 has been encountered more recently.

Case 1.—Dr. Astley Clarke's patient was a young man of 25. When he was attending his mother's funeral he was seized at the grave-side with an attack of uncontrollable laughter. He moved away feeling very embarrassed and it is not known how long the laughing continued. However, he was alarmed by the experience and went to his doctor, and subsequently he was admitted to hospital under the care of Dr. Astley Clarke. While under observation he had one or two more attacks, and these occurred without any apparent cause for hilarity, and in fact distressed him considerably. He may have presented some abnormal (e.g. ocular) physical signs, but I have now no details of them. One morning during the period of investigation he was found unconscious in bed and lumbar puncture showed that he had had a severe sub-arachnoid hæmorrhage, and he died without regaining consciousness. Post-mortem a large ruptured aneurysm was found in the interpeduncular space. Dr. Ashley Clarke made a careful examination of this and its relations after fixation of the brain; the aneurysm arose at the bifurcation of the basilar artery and extended vertically in, and in front of, the interpeduncular space, compressing the corpora mammillaria and elevating the floor of the anterior part of the third ventricle (hypothalamus). Having no photographic facilities he made

a cast of the aneurysm and adjoining structures which he subsequently sent to me, but both this and my photograph of it were lost during the war.

Case 2.—The patient, whom I saw with Dr. Majorie Blandy in 1933, was a young woman, also aged about 25, whose history was as follows: About two months earlier, while going home from work one evening as usual by train to one of the southern suburbs of London, she began to laugh, for no reason that she was aware of. The compartment was full and as the laughing went on she felt so embarrassed and distressed physically and mentally that at the next station she got out of the train; she was so convulsed with laughter that she could hardly walk and she simply went across the platform, where she held on to the railings and for several minutes simply "split her sides" laughing. She did not at all enjoy the experience and was so worried by it that she went to her doctor that evening. She was referred to hospital where Dr. Blandy on examination found no abnormal physical signs in her nervous system or elsewhere. The patient had no further attacks of laughter, but about two months later she was suddenly stricken with a severe left hemiplegia. I had an opportunity of examining soon afterwards: there was nothing characteristic about the hemiplegia and investigations had not revealed any cause for it. Nevertheless in view of this subsequent, presumably vascular, lesion, it seems a reasonable assumption that some organic disease was already present when the attack of laughter occurred.

In both of these cases the attacks of laughter preceded severe vascular lesions. Under the title *"Le fou rire prodromique"* Féré (1903) described two cases in which more frequent attacks of laughter preceded the onset of hemiplegia in elderly subjects and ceased afterwards. In one of them the attacks seemed to be brought on, *inter alia*, by mechanical stimuli; they would occur when the bus in which he was travelling ran on to irregularly paved road. In the other case the attacks had become very frequent and each was followed by an irresistible desire to sleep. The attacks of laughter were attributed by Féré to a loss of inhibitory control, but it is evident that any loss of control would have been increased by the additional lesions and so it seems that some mechanism of irritation or stimulation must have been present which was abolished at the time of the new lesions.

Case 3.—The patient, a young woman of 23 whom I first saw in October 1938, was sitting in the front row of seats at a boxing match, when one of the competitors was knocked out of the ring and fell almost at her feet. She was doubtless alarmed but it appears that she began to laugh. Her friends could not get her to stop laughing and after a few minutes took her out of the hall and subsequently she was taken, still laughing, to a hospital. According to a newspaper report her laughter was loud enough to be heard throughout the hall, and it was stated that altogether she laughed for an hour. At the hospital she was given an injection of morphia, and as she went to sleep the laughing stopped. When I saw her on the eleventh day thereafter she told an interesting story. She had no recollection of the laughing or of any incident between seeing the man fall out of the ring and waking up in hospital the next morning. In fact she was more than half inclined to believe that the reporters had made up the whole story. When she woke up in hospital she had a terrible headache and stiffness of her neck; every movement and the vibration caused by the nurses walking up and down the ward aggravated her headache and she insisted on going home. There she remained in bed for five or six days, and then, her headache gradually diminishing, she began to move about a little. When I examined her she still had some headache and a little stiff-

ness of her neck: her pupils were grossly unequal, the right one being very large, the tendon-jerks of the left arm and leg were greater than those of the right, and the left plantar reflex was indefinite, the right being normally flexor.

I asked her to obtain from the friend who had been with her an account of her behaviour at the time the laughing was going on. His report was that she simply allowed herself to be led wherever he wished; she did not speak at all, nor did she dance about or show any sign of hilarity other than the laughing. The house surgeon who saw her in the casualty department of the hospital put his hand over her mouth to try and close it to stop her laughing, and he thought that she tried to bite his hand, but as she was possibly distressed this can hardly be taken as evidence of hilarity. With the knowledge of Cases 1 and 2 I was naturally concerned for the future of this patient and as she was unwilling to come into hospital I persuaded her to put herself under the observation of a doctor. During the next few months she had frequent headaches, but no more attacks of laughing, and after the outbreak of War I lost contact with her. She had not recovered any memory of the attack of laughing or of the events associated with it. A Wassermann reaction was negative.

I presumed that this patient had an aneurysm on the circle of Willis from which a small hæmorrhage had occurred. Considering the large pupil on the right side, the most probable site of the aneurysm would be the right posterior communicating artery.

In the foregoing case a prolonged attack of laughing occurred evidently simultaneously with a sub-arachnoid hæmorrhage, but in other instances such an attack may accompany a vascular lesion which is intra-cerebral. Many years ago I saw a young man in whom the onset of a severe right hemiplegia was accompanied by immoderate laughter; subsequent investigation showed that the Wassermann reaction was strongly positive. Badt (1927) reported two cases in which laughter similarly accompanied the onset of hemiplegia due evidently to intra-cerebral lesions. The most dramatic case in the literature, however, is that described by Andersen (1936) in which the patient, a woman of 58, to all intents and purposes "died laughing." She was already suffering from pseudo-bulbar palsy, and one morning she had a sudden violent headache and within a few seconds her eyes turned strongly upwards and at the same time she was seized with a fit of laughing. She was shaken by laughter and could not stop: short expirations followed each other in spasms, without the patient being able to make an adequate inspiration; she became cyanosed and broke out in a sweat, and at times brought her hand to her throat as if she was choking. Nothing that she could do would stop the spasm of laughter, and even an injection of morphia was without effect. The laughter went on for an hour and a half. Her eyes meanwhile remained turned up and she was unable to close them. She remained conscious and could carry out instructions given by the doctor, but she was not able to utter a word. At the end of an hour and a half she lay down exhausted, in a state of asphyxia; the laughter still persisted but was noiseless and little more than a grimace. Suddenly she collapsed

and became unconscious, and after twenty-four hours of profound coma she died. Post-mortem examination showed an extensive hæmorrhage which was approximately symmetrical, and seemed to have originated from an ascending branch of the posterior communicating artery; the third ventricle was filled with blood and the hæmorrhage had spread throughout the basal structures on both sides, extending laterally to the basal ganglia and posteriorly to the thalami. Andersen realized that this case was different from those of excessive laughter from loss of inhibitory control and that the manifestation was devoid of any psychological cause and was immediately due to the hæmorrhage. He also realized that what occurred was only the "mechanism of laughing": but he attributed it to suppression of an inhibitory mechanism.

In the cases which I have referred to so far the attacks of laughing were associated with different kinds of vascular lesions. In the following case the nature of the disease is uncertain; it seems most likely that it was disseminated sclerosis but it may possibly have been a progressive lesion of other variety at the top of the brain-stem.

Case 4.—A. S., a lad, aged 18, first seen by me in 1948. Three years earlier he had suffered from weakness of his right side with ataxia of the affected limbs. When admitted to the London Hospital at that time he started laughing at times "for no reason at all": "there was nothing funny." His condition improved somewhat in the course of a few weeks, but he had various aggravations which led to subsequent admissions to the hospital for short periods. The outstanding physical signs were: pallor of both optic discs, gross nystagmus, right hemiparesis and intention tremor. The cerebrospinal fluid on one occasion gave a weakly "paretic" Lange curve, but was otherwise normal.

During the first half of 1948 he had been laughing without reason a lot more than before, and during this period he had had two attacks of fainting, though he thought he had not completely lost consciousness.

When first seen by me he was having an attack of laughing, which he was obviously trying to suppress: the laughter was not "hearty" but was always partly subdued and emerged as successive bursts or ripples of laughter. Suddenly it stopped and he answered with a seriousness and intelligence that were in surprising contrast to his immediately preceding behaviour. Then the laughing recommenced and it continued with very brief intervals for the next ten minutes or more. When he gave his history to the house physician and during his physical examination no abnormal laughing occurred though attempts were made to excite it; on two occasions during his stay in hospital he was examined by the psychologists and there is no mention of laughter or any abnormal emotional state in their reports. On the other hand he laughed frequently while lying at rest, whether awake or asleep. Both optic discs showed some pallor of their outer halves, with normal visual fields; the pupils were normal; there was coarse nystagmus with full lateral and with upward deviation of the eyes; the jaw-jerk was present and there was slight weakness in voluntary movement of the right side of the face. The right arm was so weak that it could not be raised voluntarily; it was not as well grown as the left arm, and was moderately spastic, with typically exaggerated tendon reflexes. In the left arm no abnormalities were observed. The right leg showed considerable spastic weakness and was not quite as well developed as the left; the left leg had normal power and tone, but its tendon-jerks were somewhat brisk, though much

less than those of the right; both plantar reflexes were extensor. No abnormality was discovered in the vascular system, abdomen, lungs or elsewhere. The cerebro-spinal fluid was normal and the Wassermann reaction was normal both in the fluid and in the blood. An arteriogram performed by way of the left vertebral artery showed no abnormality; a ventriculogram and electro-encephalogram also gave normal results. During his first stay in hospital, which lasted three weeks, the boy had several mild attacks of vertigo.

Six weeks after his discharge the patient was readmitted. He was then suffering from vertigo which had been present continuously for four days and in other ways he had become worse. His laughing, however, had almost stopped and he had become very drowsy. His intelligence seemed unimpaired. The abnormal physical signs were the same as before except that he now had a fine spontaneous nystagmus with his eyes in the central position. He was still able to laugh when amused. During the next four weeks the boy became progressively more drowsy and gradually passed into coma, and eventually died. Nine days before his death it was noted that he still smiled fatuously but that no audible laughter had been observed for several days. Post-mortem examination was refused.

This boy suffered from some progressive disease—probably disseminated sclerosis—which involved the uppermost part of the brain-stem. The prolonged period of drowsiness and coma lasting for four weeks before his death suggests very strongly that the hypothalamus was progressively affected. The gradual cessation of his attacks of laughter suggests either that some centre of other structure which was concerned with laughter was gradually destroyed by the disease or alternatively, that the increasing drowsiness was sufficient to inhibit the laughter, but it must be observed that the attacks of laughter had previously occurred during sleep.

I have been able to find in the literature only two cases in which fits of laughter (as distinct from uncontrolled laughter) were associated with organic disease other than vascular.

Dott (1938) described briefly the case of a little girl, the subject of pubertas præcox, who suffered from frequent fits which were always preceded by a long aura of "uncontrollable and meaningless" laughter. The child died of scarlet fever at the age of 8½, and the post-mortem examination revealed a large tumour (astrocytoma) which arose from the floor of the hypothalamus and extended down in the interpeduncular fossa. Although this tumour arose from above and was of much greater lateral extent, it is apparent from the illustration that its central part occupied much the same position as the aneurysm in Astley Clarke's case (Case 1). Professor Cappell has kindly allowed me to have pathological details of this case and to see the photomicrographs. The portion of nervous tissue damaged by the tumour was confined to that part of the floor of the third ventricle (hypothalamus) between the posterior wall of the tuber cinereum and posterior margins of the mammillary bodies. All the nuclear masses in the sides of the hypothalamus were intact and even in the corpora mammillaria most of the cells remained.

Gerard-Lefebvre (1939) described the case of a boy of 12, subject to attacks of laughter, in which X-ray examination revealed that the pituitary fossa was much enlarged, and there were some indications of raised intracranial pressure. The attacks of laughter occurred without any recognizable stimulus, and although the boy remembered them, he said he was only half-aware of them at the time they were going on, and quite incapable of controlling them. Such behaviour in school was entirely foreign to his character. The attacks were at first treated as epileptic equivalents, but without success, but when the signs of tumour were discovered radiotherapy was begun and the attacks ceased almost immediately. It may be observed that in view of the evidence of increased intracranial pressure, the lesion must have extended up into the cranial cavity, and it probably elevated the floor of the anterior part of the third ventricle (hypothalamus) since that is the usual mechanism by which a rise of intracranial pressure is brought about by tumours in the neighbourhood of the pituitary fossa.

Finally, there is a remarkable observation by Foerster, recorded by Foerster and Gagel (1933); they relate that on one occasion (Fall 4) when Foerster was trying to swab blood from the floor of the third ventricle after removal of an intra-ventricular cyst, the patient suddenly burst out laughing, whistled, made jokes and uttered obscene remarks; thereafter every time the surgeon introduced his instrument (from above) into the third ventricle and wiped coagulated blood from its floor, the patient burst into laughter and a torrent of words was released: as soon as the manipulations ceased absolute quiet was again restored. In this instance, since the patient made jokes and showed other signs of hilarity, we must judge that appropriate emotion accompanied the laughter, and the manifestations were, in fact, regarded as manic.

Comment

The first striking fact in this group of cases is that all the patients were young subjects, whereas in cases of uncontrolled laughter due to removal of inhibitory control the patients are mostly middle-aged or elderly.

All the patients were abruptly seized by these attacks, which might be maximal at the beginning. There was no indication that the attacks depended on any gradual loss of control, such as occurs with cerebral arteriosclerosis or pseudo-bulbar palsy or amyotrophic lateral sclerosis.

What occurred was a form of laughter, which the patient (if conscious) tried to suppress. In every instance the patients were surprised and in some cases alarmed by the attacks; in no case, with the possible exception of the third, was there any cause for hilarity, nor did the patient as far as could be determined, feel any emotion appropriate to laughter. Where attacks occurred under observation no exciting cause could be discovered.

It seems to me that the only satisfactory explanation of these attacks is that they are true fits—i.e. the result of abnormal discharge of the cells of some motor centre for laughter. The discharge is abnormal in that it is excited not by any physiological stimulus but, presumably (since organic disease is present), by some vascular or chemical or physical effect of an adjacent lesion. In this way it corresponds to a Jacksonian fit.

It is of the greatest interest and importance to determine the patient's emotional state during such an attack. In Cases 1 and 2 I think we must conclude from the patients' subsequent behaviour that they were not amused, and in Case 1, from Dr. Astley Clarke's account, later attacks, which occurred while the patient was under observation in hospital, came on without any recognizable cause and therefore as far as could be seen without any hilarity being aroused in the patient. In the case of the girl who began to laugh at the boxing match (Case 3) the circumstances are different, particularly in that she was not fully conscious during the attack and had no recollection of it afterwards. As she herself was unable to give any account of her feelings during the attack, the only way of judging her emotional state is from the statements of those who observed her, and there is no evidence that, apart from her laughter, her behaviour exhibited any signs of hilarity. This is perhaps the more significant because as the result of her disturbance of consciousness she would be less likely to inhibit her conduct.

Case 4 provided opportunities of making personal observations, the boy having periods in which his laughter was practically continuous. He had a way of shaking his head as he tried to stop it, and suddenly he would answer quite seriously and with full intelligence a question that had been addressed to him. The abruptness of the change was startling and quite convincing that he could not, a moment before, have been convulsed with real mirth. From this seriousness he passed again to partly suppressed laughter. At the International Congress of Neurology in Paris in 1949, Hess showed a film of ambulant cats exhibiting "rage"[1] in response to electrical stimulation applied to the hypothalamus by means of electrodes fixed in the head; an animal walking across the room with back arched, legs stiff, bristles erect and eyes glaring, when it passed out of the electric field continued to walk across the room appearing completely indifferent, the signs of rage having immediately subsided. The change in the boy I refer to was almost as sudden and as startling in its way as that in Hess's cats. It seemed impossible that emotion could be so suddenly controlled and the boy himself said that he did not feel he wanted to laugh. His attacks may be described as "sham mirth."

[1]Hess (1950) has recently expressed the opinion that the rage in these intact animals is real.

We must not lose sight of the possibility that the patient might, with his attack of laughing, feel the emotion appropriate to laughter, but might at the same time, realize by his intelligence that the emotion and corresponding behaviour were inappropriate to the environmental circumstances and try to suppress them, and feel embarrassed by the exhibition of laughter. Wilson came to the conclusion that his patients suffering from prolonged uncontrolled laughter really enjoyed their laughing even though embarrassed by it. In none of the cases that I have cited is there any evidence to support such a suggestion; what would be likely to happen if the patients really did feel hilarious is shown by the behaviour of Foerster's patient, and of my patient who had a meningioma between her frontal lobes, and the contrast between the two groups of cases is striking.

Dott described the laughter in his case as "meaningless"; Andersen made it quite clear that his patient was in a state of great distress.

It seems most probable that, in general, at their onset and throughout their duration, the attacks I am concerned with are independent of the normal emotional or effective association of laughter and the corresponding stimulus. What is exhibited is merely the "hollow" external manifestations of mirth, not backed by any appropriate emotion and, in fact, the patient's emotion may be quite inappropriate to laughter. The manifestation is "sham mirth" or "mock laughter."

The differential diagnosis has to be made from the other categories of pathological laughter and from hysteria. The precise category into which the pathological laughter falls may not be easy to determine. In elderly subjects uncontrolled laughter due to release of the laughter mechanism is much the most likely; the same applies to young subjects with extensive cerebral disease (c.f. Davison and Kelman, 1939) but otherwise such attacks in young subjects are more likely to be fits. It may not be possible during the attack to determine the patient's emotional state, but if the attacks are fits it will subsequently be discovered that the emotional state is not that appropriate to laughter. The next question is whether the fits are "idiopathic" or due to organic disease, and that may only be decided after the most thorough neurological investigation and possibly, if time is given, a period of observation.

Hysterical laughter occurs in plays and novels and doubtless also in real life after a period of high emotional tension. In several of the cases described above, the laughing was at first regarded as hysterical and if excessive laughter begins under conditions associated with strong emotion, as at the grave-side, this is a natural error. The patient is the more likely to be regarded as hysterical if she has amnesia for the period of the disturbance (Case 3), but in most cases of laughter due to organic causes the possibility of an organic basis for the attack only requires to be realized

for the error to be avoided. It is at any rate essential that a thorough neurological examination be made as soon as that is possible, and the Wassermann reaction should also be tested.

In my first case the lesion present was an aneurysm, which extended up from the top of the basilar artery to elevate and indent the floor of the third ventricle (hypothalamus). In Case 3 what occurred was probably a small hæmorrhage from an aneurysm on the posterior part of the circle of Willis, and therefore lying just below the hypothalamus. In Andersen's case there was extensive hæmorrhage, which was considered to have come from an ascending branch of one posterior communicating artery, and, if so, it must have begun close to the hypothalamus: the turning up of the eyes also suggests that the floor of the third ventricle was "irritated" at an early stage of the bleeding. In Dott and Cappell's case the tumour actually arose from the floor of the hypothalamus. In the case of Gerard-Lefebvre the pituitary fossa was enlarged, presumably by a tumour, and as there were indications of increased intracranial pressure the lesion must have extended up and probably elevated the floor of the hypothalamus, that being the usual mechanism by which rise of intracranial pressure is brought about by tumours in this neighbourhood. Thus in every one of these cases in which there were indications of the sites of the lesions, the latter, though of different natures, were so placed as to affect the hypothalamus. The association of sleep with the attacks in one of Féré's cases is suggestive of a similar localization, and the same applies to my Case 4, though in it there may have been more than one lesion. In Case 2 there was no adequate evidence of the site of the lesion but neither was there anything inconsistent with the suggestion that the hypothalamus may have been affected.

If I am right in the view that these episodes of laughter were fits, and if we are to associate them with the presence of the organic lesions (as we surely must) then it seems probable that the centre which discharged must lie in or close to the hypothalamus (or be very directly affected by it). To that extent these cases give practical support to the previous surmise regarding the site of the motor centre for laughter. Dott's case in which paralysis of laughter occurred provides further evidence to the same effect since the lesion in that instance also was one which must have affected the hypothalamus.

Another feature of these cases and by no means the least interesting is their sinister character. In Case 1 the attacks of laughter were soon followed by death, in Case 2 by a severe hemiplegia, the patient in Case 3 had the threat of further subarachnoid hæmorrhage overhanging her, in Andersen's case the laughing led immediately to coma and death and in my Case 4 it led to coma and death by slow degrees. One gets the impression from several of the cases that the "laughing centre" must lie close

to vital structures—as it would in the hypothalamus. The laughter is a mock or sham and it mocks the laughter at the time, but this is the greatest mockery of all, that the patient should be forced to laugh as a portent of his own doom.

Summary

Four cases are described in which attacks of laughter occurred in association with organic cerebral disease, and similar cases from the literature are quoted. The episodes of laughter are considered to be fits comparable with Jacksonian (motor or sensory) fits.

The patient's emotional state at the time of such an attack is not that appropriate to laughter—the apparent mirth is "sham."

In every case in which there were indications of the site of the lesion it was so placed that it might affect the hypothalamus, and these cases give practical support to the view that the motor centre for laughter is situated in or near the hypothalamus.

The observations on the patients' emotional states suggest that the centre which discharges is a motor centre and not one exciting emotion.

The attacks of laughter in most of the cases were of evil omen.

Acknowledgments

I owe my first knowledge of the subject and the material of Case 1 to Dr. Astley Clarke and I am sorry this paper was not published during his lifetime.

I wish to thank Professor Cappell to whom I am indebted for particulars of his case (partly described by Dott), and Dr. J. R. Ellis, of the medical unit at The London Hospital, to whom I owe notes of the early stages of Case 4.

BIBLIOGRAPHY

Andersen, C. (1936) *J. Belge, de Neur, et de Psych.*, **36**, 223.

Badt, B. (1927) *Zschr. f. d. ges. Neur. u. Psych.*, **110**, 297.

Bard, P. (1928) *Amer. J. Physiol.*, **84**, 490.

Brissaud, E. (1895) Leçons sur les Maladies Nerveuses. Paris.

Clarke, Astley (1931) *Brit. Med. Jour.*, **2**, 209.

Davison, C., and Kelman, H. (1939) *Arch. Neur. and Psych.*, **42**, 595.

Dott, N. (1938) The Hypothalamus. London.

Féré, C. (1903) *Rev. Neur.*, **11**, 353.

Foerster, O., and Gagel, O. (1933) *Zschr. f. d. ges. Neur. u. Psych.*, **149**, 312.

Hess, W. R. (1949) IV^me^ Congrès internationale neurologique. (Rapports) Paris.

—— (1950) Helvetica physiologica ü pharmacologica Acta, Suppl. VI Symposium über das Zwischenhirn. Ed. VII.

Lefebvre, Gerard (1939) *Bull. Soc. Pediat. de Paris*, **37**, 320.

Lopen-Aydallo, and Sempan (1932) *Anales de Medicina int.*, **1**, 999.

Marchand, L., and de Ajuriaguerra, J. (1948) Les Epilepsies. Paris.

Rothfeld (1928) *Zschr. f. d. ges. Neur. and Psych.*, **115**, 516.

Roubicek, J. (1946) *Jour. Ment. Sci.*, **92**, 734.

Wilder, J. (1931) *Der. Nervenartz.*, **4**, 75.

Wilson, S. A. K. (1924) *J. Neur. and Psych.*, **4**, 299; and (1928) Modern Problems in Neurology, London.

THE CEREBRAL BASIS OF CONSCIOUSNESS[1]

BY

W. RUSSELL BRAIN

I HAVE chosen consciousness as the subject of my address this evening because I think it may be useful to attempt to make a broad survey of some aspect of neurology. Research necessarily proceeds piecemeal, for it has to concern itself with specific problems, but in these days, when we are learning so many new facts of so many different kinds, it is a good thing that from time to time we should stop to consider how far the various pieces of the jigsaw are fitting together, and what kind of picture they are making. If the action of the nervous system is integrative, it is doubly desirable that we should try to integrate our knowledge of it.

What do we mean by consciousness? Consciousness is not something which we can define in terms of anything else: we can only indicate its meaning denotatively, that is by pointing to instances of it. When I hear a sound or see a colour, remember something, experience an emotion or think, I am conscious. Consciousness is a quality which these states, which we call conscious states, have in common, but there is no reason to suppose that it exists independently of them. There is no such thing as consciousness apart from conscious states, any more than there is redness apart from red objects. This may seem obvious, but it leads to the conclusion that we can study consciousness only by studying conscious states and that we may be able to learn about it from any state in which it is manifested. My object in this address is to try in part to answer the question: what is happening in the nervous system when we are experiencing a conscious state? I do not propose to discuss why changes in the nervous system are associated with consciousness.

LOCAL SIGN IN SENSATION

Let us begin by considering what is involved in the simplest possible experience of a bodily sensation, a touch let us say, on one big toe. It is generally agreed among neurophysiologists that although impulses in the afferent nerves differ somewhat in their rates of conduction there is no substantial difference between them corresponding to differences of sensory quality. The impulses in the optic nerve, auditory nerve and a cutaneous

[1]The Presidential Address to the Neurological Section of the Royal Society of Medicine, October 1950

sensory nerve, for example, are on the whole much the same. It is unlikely, therefore, that it is the character of the electrical impulse in the afferent nerves which tells us that we are being touched, and there is certainly nothing toe-like in the afferent impulses carried by the pathways conducting the sensations of touch from the toe which tells us that it is the toe which is being touched. No doubt, as Bishop (1946) and le Gros Clark (1947) point out, the fact that each sensory spot in the skin is supplied by branches of several nerve fibres conveys information of some localizing value, but it is information which must be interpreted centrally. The anatomist may be able to identify the toe area by tracing pathways of degeneration, the physiologist by detecting the response of the cortex to peripheral stimulation, but this is information derived from the outside: both these external observers know to start with that the impulses come from the toe. The clinician and pathologist observe that a lesion in a certain area of the sensory cortex causes a loss of feeling in the toe, but this does not explain why it should be so. If we imagine the nervous pathways from the toe to the cortex completely isolated from the rest of the nervous system, it is clear that they could by themselves convey no localizing information, for how could electrical impulses exactly like those going to all the other cortical sensory areas mean that something is happening to the toe? This surely provides a clue to the answer, which is that we can localize touch only by perceiving it in relation to a representation of the body as a whole—whether in the form of unconscious schema or fully conscious image is unimportant for our present purpose—and this body-schema maps out, as it were in a set of co-ordinates, all the possible voluntary actions which we should need to take in order to remove the stimulus either with the other foot or with either hand, or in any other way. Evidently, therefore, to perceive a part of the body as pricked is to perceive it in relationship with the whole of the rest of the body, pin-pointed as it were upon the body-image, and this process is something that happens to the raw material of the sensation of touch before it is presented to consciousness. Head, therefore, was wrong, as Walshe (1948) has pointed out, in supposing that there is any distinct pathway for tactile localization in the spinal cord, for localization is something superimposed upon the appreciation of touch. It is possible as a result of a cortical lesion for the patient to be aware of a touch without knowing where he has been touched, difficult though this is for the normal person to imagine. In other words we can appreciate touch without knowing its whereabouts, but we cannot know a whereabouts that is vacant of any sensory content.

This process of localization of touch is a cortical function, but if I am

right in thinking that it relates the touch felt to the body-image as a whole, it must involve pathways far more extensive than the primary sensory areas for touch in the cortex. When, therefore, the cortical area corresponding to one great toe is excited by the arrival there of an afferent impulse resulting from stimulation of the toe itself, such excitation must cause a widespread irradiation of impulses linking the toe area with the parieto-occipital areas which are concerned with awareness of the body-image, not only in the same cerebral hemisphere but by way of the corpus callosum with the corresponding area on the opposite side of the brain. The same thing must happen if the cortical sensory area is excited by an epileptic discharge or by an attack of migraine. The resulting hallucination of numbness referred to some part of the body cannot be the result of a discharge limited to the postcentral cortex. Paradoxically in order that it may be localized it must irradiate to the anatomical basis of the body image. And this, I take it, was what Hughlings Jackson (1931) meant when he said "I must submit that the units making up that division of the highest centres which I call the anatomical substrata of subject-consciousness represent (properly rerepresent) all parts of the body, mainly sensorily, *in relation to one another.*" And again, speaking of a prick on the back, "physically, the nervous impulses starting from a point on the periphery pricked 'travel' to units of the highest centres *universally* representing, and not to units representing one part of the back only. . . . In general the anatomical substrata of subject-consciousness are centres of universal co-ordination, or, as we said, they are unifying or synthesizing centres." Hence, when we speak of a part of the body as being represented for purposes of sensation at a certain point in the postcentral convolution on the opposite side, we do not mean that the consciousness of a part of the body is in some way localized there but that the cortical area in question constitutes a nodal point at which the sensory impulses coming from a particular part of the body are brought into relation with the whole body-image by means of pathways which must ramify widely throughout the posterior halves of both cerebral hemispheres to reach Jackson's division of the highest centres, the "anatomical substrata of subject-consciousness" rerepresenting all parts of the body in relation to one another.

So far reflection takes us. Is there any physiological evidence in favour of such a view? Adrian (1940, 1941) and Woolsey and his collaborators (Woolsey and Fairman, 1946, Woolsey, 1947) by using electrocorticography to map the responses to sensory stimulation have demonstrated the existence of two cortical sensory areas in each hemisphere, which they call somatic areas 1 and 2. Area 1 which appears to correspond to the postcentral cortex in man is strictly contralateral in its representation except

for a bilateral representation of the face area. Area 2 represents both sides of the body, but the contralateral twice as much as the ipsilateral. French, Sugar and Chusid (1947) have shown that area 2 has connexions with the pre- and postcentral areas of the same and the opposite hemisphere. Here, then, are two sensory cortical areas in each hemisphere each receiving impulses by a separate path from the thalamus, the one concerned almost exclusively with impulses from the opposite half of the body, the other intimately linked not only directly with both halves of the body, but also with the primary sensory areas of both hemispheres. We do not yet know the function of the somatic area 2, but it is tempting to believe that it is concerned with the relation of primary sensory stimuli to the body-schema. Rasmussen and Penfield (1947) have found evidence for the existence of a second sensory area in man, in a small proportion of patients and have also demonstrated the bilateral representation of the face in the postcentral cortex, a fact which explains why numbness on both sides of the mouth is a common symptom of unilateral postcentral excitation in migraine or epilepsy.

Imagery and Memory

A good deal has been written recently about disorders of the body-image itself and the main facts are now generally known. The most bizarre of these is the failure to attend to, or in extreme cases even to recognize as part of the body, the limbs on the left side as a result of a lesion in the right parieto-occipital region. One such patient dried only the right side of the body when he had a bath. There is one important conclusion which it seems to me can be drawn from cases of this kind. The surprising thing about them is not that the patient should be unable to feel one half of the body normally, but that he should apparently have forgotten that he ever possessed it. He not only disregards it but he does not know that he is disregarding it. We can only miss something if we can remember that we once had it. I conclude, therefore, that the lesion in such cases has destroyed not only the patient's present awareness of his body-image but also neurones which are essential to his ability to remember that he ever possessed a left half of the body. If this is a true interpretation it would seem that the process of remembering the body-image involves an activation of the same neurones as are concerned in its current awareness, and this I suspect may be generally true. The remaining half of the bisected body-image seems to constitute itself a new Gestalt, and consciousness, having lost the memory of the left half of the body, is unaware of the incompleteness of what remains. The comment is often made that these patients, of course, are mentally abnormal and this is sometimes put forward as an explanation of these peculiar psychophysio-

logical phenomena, but this may be to invert cause and effect, for the body-image plays a very important part in our sense of identity, and a patient who has lost half of his body-image has suffered so severe a mutilation of the psychophysiological basis of his ego that it is not surprising that he should become mentally disordered.

What happens in the brain when we exercise visual imagination, when we create a visual image of some past event or even of something purely imaginary? Electro-encephalography provides a clue in the fact that the exercise of the imagination interferes with the alpha rhythm which is regarded as indicating a state of rest in the visual cortex. Grey Walter (1950) concludes that "this suggests that those cerebral regions which were previously responding regularly to the external stimuli are mobilized for internal service when the attention is directed to an imaginary problem—it is possible, therefore, that imagination involves the projection of an internally constructed assembly of data upon the same area as is otherwise used for the processing of 'real' or external information before the pattern can be recognized and used for the miniature experiment of thought." If this be true, isolated destruction of the whole visual cortex should destroy the capacity for visual imagery. Does this occur?

Lashley's (1943, 1950) experiments with rats show that those animals which have been taught to find their way through a maze could still carry out this task after removal of any area of the cerebral hemisphere except the visual cortex. Moreover, Lashley has shown that when blind animals are trained in the maze the removal of the primary visual cortex produces a severe loss of the habit with serious difficulty in relearning, although the animals could have used no visual cues in the initial learning. He suggests that "a possible explanation of this curious effect was that the rat formed concepts of spatial relations in visual terms, as man seems to do, and that the space concepts are integrated in the visual cortex. The visual cortex might then function in the formation of spatial habits, even when the animal loses its sight."

It sometimes happens that as a result of a lesion of the brain a patient loses all visual imagery, which can no longer be evoked voluntarily and ceases to occur spontaneously. This condition has also been called loss of revisualisation (Nielsen, 1946). One such patient of mine showed a number of interesting features.

A male, aged 36, sustained a severe head injury with a depressed fracture in the mid-frontal region. When seen five years later his sole complaint was that he had "lost his picture memory." Previously a good visualizer he could no longer visualize anything: he could not form a mental picture of people he knew intimately, but he could still recognize people, even when he had only seen them once before, and he could still describe people and objects even though he could no longer visualize them. He was a builder's manager and he was still able to work

although, because he could no longer visualize a plan or an elevation, he had to keep referring to the specification. He built his own house by remodelling four cottages and he would work out all the alterations on a plan at night and would then inspect the work next day in order to correct any mistakes he had made in the plan. He could no longer picture routes, and if going on a journey which he had travelled before he had to look up maps and trace the route afresh. He still recognized landmarks when he came to them. He said that the character of his dreams had changed, a fact which he described as "rather uncanny." "When I dream," he said, "I seem to know what is happening, but I don't seem then to see a picture. I can dream about a person without seeing him." He could no longer visualize his own body. His only speech difficulty was concerned with spelling, which he attributed to an inability to visualize the words. His visual acuity and fields were normal.

Thus there was no evidence in this case of a lesion in the visual cortex. Nielsen states that the lesion responsible for loss of revisualization involves Brodmann's area 19. Pitts and McCulloch (1947) state that during stimulation of a single spot in area 18 "human patients report perceiving complete and well defined objects, but without definite size or position, much as in ordinary visual mental imagery" (*see also* Bonin, Garol and McCulloch, 1942). We do not yet know enough about the functions of the parastriate region to be dogmatic, but there is evidence which suggests that visual imagery may depend upon the integrity of that part of the brain, which in my patient may well have been damaged by a contre-coup lesion. Whether the image is, as it were, displayed upon the visual cortex or utilizes a secondary visual area we do not yet know.

In the case cited the functions preserved are as interesting as the functions lost. The patient could recognize objects normally, though he could no longer visualize them, and he could also describe them from memory. Thus, in his case at any rate visual imagery played no part in visual recognition and it is possible to have what I may term a propositional memory of things which cannot be visualized. Here we have a very precise experiment on the value of consciousness compared with unconscious mechanisms in the visual sphere—a point to which I shall return.

Penfield's (1947) observation that it was possible to evoke in a patient an elaborate visual picture of a remembered scene by electrical stimulation of the temporal lobe takes us a step further towards the anatomy of memory. The importance of the temporal lobe for memory has long been familiar on account of the disturbances of memory which accompany uncinate fits. Apart from that, pathways evocative of memory originating in the temporal lobes seem to be implied by the fact that words can evoke memories. When I say: "Do you remember so and so"? I am exciting an impulse in your temporal lobe beginning in the auditory cortex and perhaps leading you to create visual images. So we seem led

to picture the anatomical basis of memory, so far as it involves images, as innervating widespread areas of the cortex, including in all probability the relevant primary sensory areas. Dreaming must involve in part the same pathways. Clearly it would be quite erroneous to picture either memories or images as "stored" in some area of the brain. We should think rather of a widespread neural network which can be set vibrating in an almost infinite variety of patterns in space and time.

Consciousness and Patterns

One of the most fundamental properties of the brain is that which renders possible the recognition of patterns. The biological importance of this is obvious on a little reflection. Objects of the same kind differ among themselves. Cats, for example, are not all alike. Survival, however, often depends upon the ability of the organism to react to all objects of a class in the same way. Clearly it would be impossible for the nervous system to be so organized that the appropriate reaction should be directly linked with each group of stimuli representing each of the various individuals of a given class. The organization required would be too complex. Such reactions could not be innate nor could they be learned by experience, because each fresh individual member of the group would constitute a new group of stimuli, the reaction to which had not previously been learned. If a mouse is to succeed in recognizing and reacting appropriately towards a cat it must do so the first time or not at all, and it cannot afford to make the mistake of recognizing black cats as cats but not white ones. The nervous system has solved this problem in what would seem to be the only possible way: it has introduced plasticity into the receptive side so that what the animal reacts to is not a mosaic of all the individual features of the object perceived, but a pattern which constitutes an abstraction from any particular individual, but for that very reason is common to all individuals of the group. Thus, for example, a rat can be trained to recognize, on the sense of reacting in a trained manner to, triangles as distinct from other geometrical figures. Field experiments on the recognition of predatory birds by the small birds on which they prey (Hartley, 1950, Lorenz, 1940, Kratzig, 1940) have shown that in several species the recognition of a hawk depends entirely upon the combination of two visual characters, outline and movement. A generalized silhouette has been produced which in birds, such as ptarmigan, causes fear reaction when moved in one direction, when it is, apparently, taken for the short-necked silhouette of a hawk, and no more than attention when moved in the other.

In this connexion pattern is a general term of wide application and it usually stands for something much more complex than the instances

which we have just considered. Thus, visual patterns may take into account not merely outline but also light and shade and, as we have seen, movement, and patterns can be discovered by other senses than vision: a musical tune, for example, is a pattern which is extended in time and which remains the same whatever its key and whatever the instrument on which it is played. As I have pointed out (Brain, 1950) the recognition of words in speech involves an identical physiological process. We recognize a word when we hear it spoken by any person with whatever accent, at any pitch and whether shouted, whispered or sung. Similarly we recognize it when we read it, whatever the size or character of the type in which it is printed and whether the print is coloured or black. In other words we recognize a pattern which underlies all the auditory stimuli involved in uttering a particular word, though from a physical point of view and even from the point of view of stimuli which they produce in the auditory cortex they must in most respects be different from one another. In the same way we recognize some common patterns in all the visual representations of a single word. This process is unconscious, for there is no single group either of auditory or of visual stimuli into which we translate all the different ways of uttering or writing a word before we can understand it. The word, however expressed or written, is at once recognized as being the same word—as possessing, that is, the same meaning. So between various ways of expressing a word and our recognition that it is the same word with a single meaning there must exist a process in the nervous system which abstracts from the complex of the stimuli a pattern common to them all. And in man we can take the process much further, for not only is there such a pattern through which we recognize a word we hear and another pattern through which we recognize a word we see, and these in turn must submit to a similar process at a higher level by which we reach a conception of the word as an element in thought, and words again are grouped into the patterns which constitute sentences which underlie propositional speech, and it would seem that abstract thought itself need involve only the same physiological process at a higher level and in greater complexity.

Various views have been put forward (Lashley, 1942, Brain, 1950) as to what this process is. My own suggestion is that a modification of the concept of the schema put forward originally by Kant and introduced into neurology by Head and Holmes (1920) is the key that fits the lock, and Pitts and McCulloch (1947) have attempted to describe in mathematical terms the physiological processes in virtue of which the brain renders possible the recognition of universals. They claim no finality for their particular suggestion, but they have at least shown that, taking into account what is known of the structure and functions of the

cerebral cortex, a plausible account can be given of the physiological process which is the foundation of much of our mental life, but which operates in such a way as to present to consciousness only the end-results of its activity.

The Cerebral Basis of Feeling

I have spoken earlier about the link between feeling and representation, and this is reflected in the impossibility of making a complete physiological and anatomical distinction between the functions of the cortex and those of the diencephalon. When we react emotionally either to the perception of objects or to the contemplation of an idea there must be impulses passing between the cortex and the diencephalon and hypothalamus. We are still far from understanding the physiology of their mutual relationship, and recent work on the functions of the base of the frontal lobes and the cingulate gyri impinges upon this problem. Nevertheless, I think that Head and Holmes were right in maintaining that the conscious experiences which we call feeling are correlated with the diencephalic nuclei, particularly the optic thalamus, in the sense that we experience feelings when nervous impulses reach these parts of the brain. In the realm of feelings it is useful to distinguish those which are localized in some part of the body, such as pain, and which are termed sensations, and those which are not so localized and which are termed emotions. I experience pain in some part of my body, but I do not experience joy anywhere in particular. A parallel distinction can be made in the sphere of cortical function for I localize my perception both of the external world and of my body, but I do not localize my thoughts.

Is the localization of pain a function of the optic thalamus? The experimental work of Dusser de Barenne (1935) has revealed a previously unsuspected intricacy in the thalamus including the bilateral representation of cutaneous sensation in each thalamus, and points to what he calls "the high level of functional integration attained in thalamic activity." Though, no doubt, the relations between the sensory cortex and the thalamus are intimate, it is worth bearing in mind that the nervous impulses concerned in what Head called epicritic sensation pass through the thalamus and may therefore be capable of influencing thalamic activity at a subcortical level. It seems likely that a considerable degree of pain-localization occurs in the thalamus though the sensory cortex probably contributes greatly to the accuracy with which the site of the painful stimulus is recognized.

The Biology of Consciousness

Let us now take a few steps back from this unfinished picture and see how it looks from a biological standpoint. Whether or not the

behaviour of any organism which possesses a nervous system can be explained entirely in terms of reflex action, there can be no doubt that organisms with the most primitive types of nervous system exhibit mainly the characteristics which we have come to associate with the simpler types of reflex action, similar in essentials to those studied by Sherrington in the spinal cord of the dog. Of these I would stress two. The first is the inevitability or automaticity of response. This, of course, does not mean that the same stimulus always produces exactly the same effect, for the response is modified by the state of the rest of the nervous system at the time at which it is applied, but within these limits the response to the stimulus is automatic. Secondly, both the stimulus and the response are immediate. When we think of such reflexes we picture some kind of stimulus applied directly to the organism, as when salivation is produced by placing meat in a dog's mouth, or the orbicularis oculi contracts on touching the cornea. Even when a distance-receptor, such as the eye, is the afferent channel, as in the light reflex, we tend to think of the effective stimulus as the light falling upon the eye rather than the torch or other source of illumination in the distance. It is only in the more highly evolved animals that distance-receptors come to assume importance as reflex channels. In the case of the primitive reflex in the primitive organism the stimulus is immediate in the sense that it is not mediated, that is it is a direct contact with some part of the animal's body. The response is similarly immediate or practically so: there is no long delay between the arrival of the stimulus and the reaction of the effector organ.

We do not know whether reflex activity is ever directly related to consciousness. We are familiar with many reflexes in ourselves of which we are quite unconscious, though consciousness may be superimposed, as when we feel the touch on the cornea which causes an involuntary closure of the eye, but it is clear that consciousness could add nothing to a reaction which is the inevitable response to a stimulus.

One of the great advances in evolution was the development of what Sherrington has called distance-receptors, that is, the receptors reacting to objects at a distance. Sherrington (1947) says in "The Integrative Action of the Nervous System": "The 'distance-receptors' seem to have peculiar importance for the construction and evolution of the nervous system. In the higher grades of the animal scale one part of the nervous system has, as Gaskell insists, evolved with singular constancy a dominant importance to the individual. That is the part which is called the brain. *The brain is always the part of the nervous system which is constructed upon and evolved upon the 'distance-receptor' organs.*" The development of distance-receptors had a profound effect upon the organism's relationship not only to space but also to time. If it is to react to objects at a distance, time

must enter into the organization of its nervous system in a manner which has no parallel in the more primitive creature which responds automatically to immediate stimuli. The organism which is to react to an object at a distance must initiate a course of action which takes time, whether it is to go in pursuit of it or endeavour to avoid it. No doubt in the lowliest organisms with distance-receptors the times concerned are not very long. Nevertheless, as soon as reactions evolved which were organized in time and directed towards objects continuing in time, the nervous system came to possess potentially a type of reaction which was capable of maintaining a specific activity for an indefinitely extended length of time.

How was this done? By the development of new types of nervous function, which, though we consider them separately, are so closely integrated in action that their separation is to some extent an artificial abstraction. The first is feeling. We can, of course, know nothing about any feelings except those of human beings, our own by direct awareness and other people's by what they can tell us about them. From our own experience it seems clear that our feelings either themselves provide the motive power, or, if you prefer the term, are the manifestations in consciousness of the motive power, which sustains our courses of action in time. The time concerned may be short, as when hunger sends us in search of a meal, or indefinitely protracted as when an interest in scientific research determines the activities of a life-time. Any interpretation of animal behaviour in terms of human consciousness must be made with caution. Nevertheless, there is far less difference between a higher animal and man in respect of the diencephalic structures which we believe to be the basis of feeling than there is in respect of cortical development. Therefore, having regard to the principle of evolution, it seems likely that animals experience feelings which are associated with impulses to action whether these are comparatively short-term activities, like the pursuit of prey or the escape from an enemy, or more lengthy and elaborate proceedings, such as those concerned with the care of the young.

But, as we have just seen, feeling is directed towards an object, and if actions are to take time the organism must possess an enduring representation of that object. Here we reach the other new function of the nervous system, the representation of the external world. I do not propose to discuss the philosophical aspects of consciousness but probably most, if not all, neurologists accept what has been called "physiological idealism." All that we know about the physiology of the conduction of nervous impulses teaches us that perception only occurs when nervous impulses reach the appropriate end-stations in the brain, that these nervous impulses are all much alike and that they are quite

unlike the physical stimuli whether of light, sound or chemical character which initiate them. Our perceptions, therefore, are largely a product of the activity of our nervous systems and they are, as we say, "projected," and perceived as being external to ourselves. This, of course, has given rise to a number of philosophical puzzles, with which we are not now concerned, but if you accept physiological idealism, at any rate for physiological purposes, you will be prepared to agree that the world which we perceive is a representation of the real world created to a large extent by the nervous system, and this I would suggest to you is the function of the cerebral cortex on its receptive side.

We can go further, for if at least what the philosophers call secondary qualities, such as smells, sounds, colours and so on, are quite unlike the physical stimuli which give rise to them, then we must regard them as symbols of physical reality and say that the receptive function of the cerebral cortex is to provide us with a symbolical representation of the whole of the external world, not only distinguishing objects by their qualities, but also conveying to us the spatial relationships which exist between them, and at the same time giving us similar symbolical information about our own bodies and their relationship with the external world. All this information, of course, is given us not merely for the sake of pure awareness or contemplation, though that may sometimes be a by-product of it, but in order that we may act; hence it is linked, in ways with which we are familiar, with the motor activities of the brain. This is the element in consciousness which for convenience of brevity we may call "cortical." My patient who had lost his powers of visual-imagery illustrates very well the normal contribution of consciousness to action in providing an enduring model of the external world.

You will have noted that I have implicitly accepted the basic distinction made by Head between the sensory functions of the optic thalamus and those of the cerebral cortex, though I would add to the optic thalamus such other diencephalic nuclei as have been, or yet may be discovered to be associated with emotion, and I have, as you will have perceived, extended Head's idea of cortical sensory function. When he says, for example, that "the part played by the cortex in sensation is concerned with those physiological processes which underlie projection and discrimination," he seems to be trembling on the verge of the broader generalization that the sensory cortex is concerned with the symbolical representation of the body and of the external world and their mutual relationship.

As soon as the nervous system had acquired the power to create representations of the external world the potentiality of memory made its appearance. Learning is within the capacity of extremely primitive organisms and it is certainly possible that it may occur in the absence

of any representation of the external world, by some process of facilitation of repeated reactions, but it seems impossible that we should remember something of which we have not previously experienced a representation.

If all perception is a symbolic representation it follows that symbolization is an inherent function of the nervous system, and there is no difficulty in understanding the further step by which a hierarchy of symbolic processes occur. Thus, all speech and thought which employ symbols to represent perceptual experiences or ideas are merely a further development of the symbolic function of the nervous system. We should be wrong if we regarded such higher types of symbolization as peculiar to man. The remarkable observations of von Frisch on the honey-bee, reviewed and confirmed by Thorpe (1950) show that the worker on returning to the hive indicates to other workers a new source of food by means of a dance in which "the direction of action of gravity is symbolic of the direction of incidence of the sun's rays."

The Nature of Unconsciousness

It is sometimes stated that consciousness is localized in some particular region of the brain. Such a statement needs to be carefully defined if it is not to be ambiguous or actually misleading. So far we have been dealing with what may be called the content of consciousness and there is no evidence that any destructive lesion of the cerebral cortex, or of the subcortical white matter, or of the posteroventral nucleus of the thalamus, can do more than abolish or distort some part of the content of consciousness, though, of course, a very diffuse, destructive lesion of cortical ganglion cells, such as may occur in some forms of encephalitis, may reduce the contents of consciousness to almost nothing. There is, however, another way in which consciousness may be affected, as it were globally, so that the patient suddenly loses consciousness and almost as rapidly regains it, as in attacks of *petit mal,* or suddenly loses it and gradually regains it as a result of a head injury, or gradually loses it and as slowly recovers it as when a tumour compresses the base of the brain and is successfully removed. In cases of this kind it is not the content of consciousness which varies, but the quantum, though that in turn, of course, has profound effect upon the content.

"Unconscious" is a purely negative term: there is no such *thing* as unconsciousness, and the lesions or disorders of function which abolish consciousness may well be of different kinds. As Jefferson (1944) says, "we need to define unconsciousness, whether traumatic or otherwise, by a new term which designates more pointedly its nature, its pathological status in terms of neurophysiology." If we were to attempt to do this, even in the present state of our knowledge, we should find that several

such terms were needed. Even clinical observation alone shows that unconscious patients differ from each profoundly, a point with which we are all familiar. Not only do they vary in respect of such content of consciousness as may remain, but also in respect of muscle tone, posture, the movements of which they are still capable, the condition of the autonomic nervous system and in many other features. The patient who in an attack of *petit mal* continues to ride a bicycle is in a very different condition from a patient who lies in bed comatose from a lesion in the posterior hypothalamus. To say that both are unconscious is a half-truth which may stifle further enquiry.

Penfold and Jasper (1947) have pointed out that whereas the removal of the anterior frontal region has no effect upon consciousness, seizures beginning there abolish it from the very onset, and Jasper and Droogleever-Fortuyn (1947) claim to have reproduced experimentally the electrical phenomena of *petit mal* in cats by stimulating the intralaminar region of the thalamus. Quite different are the states of so-called hypersomnia produced by lesions of the posterior hypothalamus and I agree with Jefferson (1944) that it is desirable to use a term—he has suggested parasomnia—which indicates that this state both resembles and in important aspects differs from normal sleep. Finally both Jefferson and Cairns (1949) have pointed out that unconsciousness may be produced by lesions occupying the posterior fossa and in Atkinson's (1949) account of the symptoms of thrombosis of the anterior inferior cerebellar artery he mentioned unconsciousness or obscuration of consciousness. I can myself recall a patient who had had a suboccipital decompression and who lost consciousness as the result of pressure upon the medulla by a cystic collection of cerebrospinal fluid, and immediately regained it when some fluid was withdrawn. An even more instructive case was a man who, when 56, began to suffer from mild attacks of vertigo on getting into bed. Two years later he had attacks of giddiness terminating in loss of consciousness, without convulsion or incontinence. When these had gone on for six months he had a typical attack of thrombosis of the posterior inferior cerebellar artery. He made a good recovery and during the subsequent six years has never had another attack of giddiness or loss of consciousness.

In such cases all the evidence suggests that consciousness is impaired primarily as a result of disturbance of function of the brain-stem rather than of any remote effect upon the supratentorial structures. Various suggestions have been made as to the mechanism of the loss of consciousness in some of these cases (Grey Walter, 1947, Martin, 1949, Williams, 1950). We have still much to learn here, but it looks as though we could already distinguish at least three neurophysiological types of disturbance:

(1) *petit mal* dysrhythmia, possibly associated with a discharge from the medial portion of the thalamus; (2) parasomnia with the disturbance in the posterior hypothalamic region; and (3) a lower brain-stem disorder which, when it is more fully understood, may perhaps throw light upon syncope. There must, of course, be others. Descartes said: "I think, therefore, I am" but only a philosopher surely would indentify thought with existence. As neurologists we should not be surprised that consciousness is most intimately linked with those basal nuclei which made their appearance in the course of evolution millions of years before thought became possible, and since the days of our earliest vertebrate ancestors have sustained the life of the feelings.

REFERENCES

ADRIAN, E. D. (1940) *J. Physiol.*, **98**, 16.
—— (1941) *J. Physiol.*, **200**, 159.
ATKINSON, W. J. (1949) *J. Neurol. Neurosurg. Psychiat.*, N.S., **12**, 137.
BISHOP, G. H. (1946) *Phys. Rep.*, **26**, 77.
BONIN, G., VON GAROL, H. W. and MCCULLOCH, W. S. (1942) *Biol. Sympos.*, **7**, 165.
BRAIN, W. R. (1950) Perspectives in Neuropsychiatry. London, 127.
CAIRNS, H. (1949) Horsley Lecture (in the press).
CLARK, W. E. LE G. (1947) Anatomical Pattern as the Essential Basis of Sensory Discrimination. Oxford.
DUSSER DE BARENNE, J. G. (1935) Sensation: Its Mechanisms and Disturbances. Res. Pub. A.R.N.M.D. **15**, 274.
FRENCH, J. D., SUGAR, O., and CHUSID, J. (1947) *Fed. Proc.*, **6**, 106.
HARTLEY, P. T. H. (1950) Physiological Mechanisms in Animal Behaviour. Cambridge, 313.
HEAD, H., and HOLMES, G. (1920) Studies in Neurology, **2**, 605.
JACKSON, J. H. (1931) Selected Writings, **2**, 96–7.
JASPER, H. and DROOGLEEVER-FORTUYN, J. (1947) Epilepsy. Res. Pub. A.R.N.M.D. 272.
JEFFERSON, G. (1944) *Brit. M. J.*, **1**, 1.
KRATZIG, H. (1940) *J. Orn. Lpz.*, **88**, 139 (quoted by Hartley).
LASHLEY, K. S. (1942) *Biol. Sympos.*, **7**, 301.
—— (1943) *J. Comp. Neurol.*, **79**, 431.
—— (1950) Physiological Mechanisms in Animal Behaviour. Cambridge, 454.
LORENZ, K. (1940) *Verh. disch, zool. Ges.*, 1939, **69** (quoted by Hartley).
MARTIN, J. P. (1949) *Lancet*, **1**, 1 and 48.
PENFIELD, W. (1947) *Proc. Roy. Soc. B.*, **124**, 329.
——, and JASPER, H. (1947) Epilepsy. Res. Pub. A.R.N.M.D. 252.
PITTS, W., and MCCULLOCH, W. S. (1947) *Bull. Math.*, Physics, **9**, 127.
RASMUSSEN, T., and PENFIELD, W. (1947) *Fed. Proc.*, **6**, 452.
SHERRINGTON, C. S. (1947) The Integrative Action of the Nervous System, 2nd Ed. Cambridge, 325.
THORPE, W. H. (1950) Physiological Mechanisms in Animal Behaviour. Cambridge, 387.
WALSHE, F. M. R. (1948) Critical Studies in Neurology. Edinburgh.
WALTER, W. G. (1947) Epilepsy. Res. Pub. A.R.N.M.D. 237.
——, (1950) *J. Ment. Sci.*, **96**, 1.
WILLIAMS, D. (1950) *Brit. M.J.*, **1**, 685.
WOOLSEY, C. N. (1947) *Fed. Proc.*, **6**, 437.
——, and FAIRMAN, D. (1946) *Surgery*, **19**, 684.

A COMPARISON OF THE SENSORY DISSOCIATION PRODUCED BY PROCAINE AND BY LIMB COMPRESSION

BY

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Introduction

It has long been known that by offering to the trunk of a sensory nerve a variety of insults such as cold (Weber, 1847), pressure (Bastien and Vulpian, 1855) or cocaine (Goldscheider, 1886) a dissociation of sensibility in the cutaneous distribution of that nerve may be produced; that is to say, the four customarily recognized modalities of sensation do not become paralysed simultaneously. It has been tacitly assumed that this phenomenon is due to the way in which the agent employed attacks the fibres of the nerve trunk, and, since the demonstration by Gasser and Erlanger (1929) that nerve fibres are blocked in a manner approximately related to their conduction velocities when a nerve trunk is exposed *in vitro* to the action of cocaine or of compression, attempts have been made to associate sensory function with fibre size. However, we have recently pointed out that the order of sensory loss recorded in procaine nerve blocks in man is, in great part, if not entirely, the resultant of such influences as the area of skin tested, the intensity, size and duration of the stimulus and individual variation (Sinclair and Hinshaw, 1950). Such factors would presumably also be operative in the sensory dissociation induced by applying a compression cuff to a limb, and it was hoped that, by correlating the results of compression experiments with those of procaine nerve blocks, it would be possible to decide whether the manner in which procaine or compression blocks attacked the nerve fibres was relevant to the production of sensory dissociation or not.

Since the order of sensory loss in procaine blocks can be grossly altered by manipulation of the conditions of the experiment, no comparison could be drawn between the two types of block, unless these conditions were as nearly as possible identical in the two instances. Accordingly, it was decided to carry out procaine and compression blocks on the same nerves of the same subjects, and to use the same methods of sensory testing and experimental endpoints.

Material and Methods

In five subjects the comparison was made on the ulnar nerve territory, and in four the lateral popliteal nerve was used (figs. 1 and 2). The position

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of the numbered testing circles used is shown in figs 1 and 2, and the nature of the stimuli and the endpoints adopted are given in Table I. The

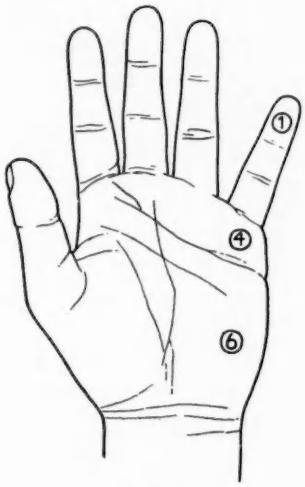

FIG. 1.

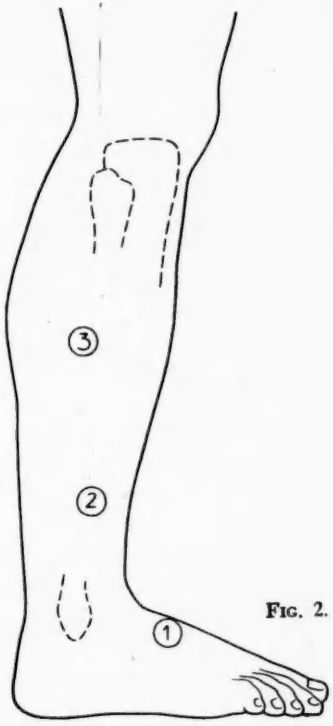

FIG. 2.

FIG. 1.—Position of numbered testing circles in the ulnar area. Each circle is 1 cm. in diameter; the numbering is that of Sinclair and Hinshaw (1950).

FIG. 2.—Position of numbered testing circles in the lateral popliteal area.

interval between one type of block and the other varied from a few weeks to a few months.

The procaine blocks were induced by the injection of 1½ to 2½ per cent procaine hydrochloride with 1:800,000 adrenalin round the ulnar nerve in the ulnar groove or round the lateral popliteal nerve at the neck of the fibula (Sinclair and Hinshaw, 1950); this was found to produce a satisfactory dissociation lasting long enough and developing slowly enough to permit of easy assessment.

The compression blocks were induced by the inflation of a sphygmomanometer cuff 12 cm. wide round the arm just above the medial epicondyle, or just below the knee-joint. The pressure in the cuff was 200

TABLE I.—METHODS OF SENSORY TESTING

Modality	*Stimulus*	*Method of use*	*Endpoint adopted*
Touch	No. 2 nylon suture material, 2·5 cm. long, mounted in metal holder 25 cm. long	Vertical punctate stimuli delivered at random within a circular area 1 cm. in diameter	3 or more out of a group of 6 such stimuli not appreciated
Pain	Round needle 12·5 cm. long	Vertical pricks just short of drawing blood, delivered at random within a circular area 1 cm. in diameter	3 or more out of a group of 6 such stimuli not appreciated *as painful*
Warm	Test-tube, 1·5 cm. in diameter, half-filled with water at 45° C. ±2° C.	Butt of tube allowed to rest by its own weight on the testing area for 10 secs.	3 or more out of a group of 6 such stimuli not appreciated *as warm*
Cold	Test-tube, 1·5 cm. in diameter, half-filled with water at 15° C. ±2° C.	Butt of tube allowed to rest by its own weight on the testing area for 10 secs.	3 or more out of a group of 6 such stimuli not appreciated *as cold*

mm.Hg., and no compression was continued longer than necessary to establish a definite order of loss of the four sensory modalities tested. In general this meant a compression period of about 30–35 minutes, but the longest compression was one of 43 minutes. The arm cuffs were applied as described by Sinclair (1948), the arm being allowed to hang vertically downwards during compression; for the leg compressions the subject lay flat on his back.

In an additional five subjects (making a total of 14 subjects used) the possibility of altering the order of sensory loss in compression blocks by altering the intensity, size and duration of the stimuli was investigated; these men did not undergo a procaine block.

RESULTS

Manner of Sensory Loss.

A characteristic sequence of events takes place within all sensory modalities during the development of both compression blocks (Sinclair, 1948; Weddell, Sinclair and Feindel, 1948) and procaine blocks (Sinclair and Hinshaw, 1950). In the case of Touch and Pain the quality of the sensation becomes altered, an increasing percentage of stimuli fail to be perceived, the response becomes delayed and prolonged, and finally anæsthesia or analgesia supervenes. These findings were confirmed in the present series, and it was found that the only difference between the two

types of block was that in the compression blocks the alteration in the quality of pain sensibility (Weddell, Sinclair and Feindel, 1948) was much more marked and unpleasant than in the procaine blocks.

The changes within the modalities of Warm and Cold were similar in both types of block, but differed slightly from those relating to Touch and Pain. Alterations in quality of temperature sensations were less common than the occurrence of paradoxical sensations, Warm being reported as Cold and vice versa. The marked prolongation of the sensation which occurred in Touch and Pain was not nearly so noticeable with temperature sensations, but on the other hand, the interval between a temperature stimulus and its perception frequently became more than twice as long as the maximum delay recorded with tactile or painful stimuli.

In the procaine blocks, the time taken to reach the "end-point" of a given modality (*see* Table I) could be markedly varied by altering the intensity of the stimulus, a stronger stimulus continuing to give a response for many minutes after a weaker one had ceased to be effective. This effect was also noted in the compression blocks, but the alteration in the timing of the end-point which could be produced by this means was smaller than in the procaine blocks.

Again, it was found in both procaine and compression blocks that the larger the surface area of a temperature stimulus the longer it would give rise to a response, and that the length of time for which a temperature stimulus was applied could affect the end-point. Thus, a warm stimulus might initially be reported as cold, but if it remained *in situ*, after a few more seconds it would be recognized correctly.

In short, it may be said that the process of disappearance of any given modality was essentially similar in both procaine and compression blocks, and the methods by which the duration of this process could be modified were the same. Subjectively, the change in quality of Pain appeared to differ in the two types of block, and objectively, the timing of the end-points could not be modified so greatly in compression as in procaine blocks. These minor differences do not suggest any reason why a direct comparison should not be made between the order of loss of sensibility in both types of block, provided that all the established disturbing factors in the conduct of the experiment are made the same in both instances. Attention was therefore turned to the order of loss of the four modalities in different skin areas. The process of evaluation of the results was exactly the same in both compression and procaine blocks, and for the sake of brevity will only be detailed for the compression blocks; the procaine results will merely be summarized.

Order of Sensory Loss in Compression Blocks of Ulnar Area.

In the five subjects used, the time taken for each modality to reach its defined end-point was recorded for each of the three areas within the ulnar territory (fig. 1), and the results were subsequently ranked in order of disappearance. If two or more modalities "failed" within two minutes of each other, they were considered as equal. Ties in the ranking were dealt with in the usual manner, by dividing the sum of the appropriate ranks equally between the tying modalities. The individual figures for each area were then summed to give the best estimate of the true rank (Kendall, 1945*b*); the results are shown in Table II. The total

TABLE II.—SENSORY DISSOCIATION IN ULNAR AREAS: COMPRESSION BLOCKS

Site of stimulation	*Touch*	*Cold*	*Warm*	*Pain*
Area 1	9½	9	11½	20
Area 4	7	15½	14	13½
Area 6	6	11	17	16
Total	22½	35½	42½	49½

The figures are the sum of the individual ranks allotted to each modality as described in the text.

ranking order is Touch, Cold, Warm and Pain in that order, but on applying to this total rank the test of homogeneity devised by Kendall (1945*a*) the coefficient of concordance is found not to be statistically significant, indicating that individual variations in ranking are too great for much weight to be attached to the result. Some of these variations occur between subject and subject, but others are found between area and area. Thus, in Area 1, Touch and Cold obtain an almost equal ranking, but in Area 4 there is a marked difference between them; again, there is little to choose between Warm and Pain in Areas 4 and 6, but a considerable difference in Area 1.

The relationships between every possible pair of modalities were then investigated by computing how many times one member of a pair had failed before the other, and how many times after. Occasions on which both failed together were divided equally between the "befores" and "afters." The results were then tested (using chi-square) against the hypothesis that one modality should not tend to fail before another—i.e. that the "befores" should equal the "afters." It was found that in these blocks Touch failed significantly more often before Pain than after it ($p < 0{\cdot}001$) and that it also failed significantly more often before Warm than after ($p < 0{\cdot}05$). No other statistically significant results were obtained.

Order of Sensory Loss in Compression Blocks of the Lateral Popliteal Area.

Similar data for the four subjects whose lower limbs were compressed are given in Table III. The totals are ranked in the order Touch, Warm,

TABLE III.—SENSORY DISSOCIATION IN LATERAL POPLITEAL AREAS: COMPRESSION BLOCKS

Site of stimulation	*Touch*	*Cold*	*Warm*	*Pain*
Area 1	5½	11½	9½	13½
Area 2	6	12½	8	13½
Area 3	5½	11	12½	11
Total	17	35	30	38

The figures are the sum of the individual ranks allotted to each modality as described in the text.

Cold, Pain, but again the coefficient of concordance is not statistically significant. The differences between individual areas are here much less noticeable than in the ulnar blocks, indicating that most of the variation occurs between subjects. When pairs of modalities were compared it was found that Touch failed significantly more often before both Pain ($p < 0.01$) and Cold ($p < 0.01$) than after them, but no other significant figures were obtained.

The figures for the relationship of given pairs of modalities in the lateral popliteal area were then compared statistically with those for the same pairs in the ulnar area; no significant difference was found. It was therefore thought worth while to examine the result of combining the data from both ulnar and lateral popliteal blocks. If this is done, the overall rank—Touch, Cold, Warm, Pain—now becomes significantly concordant ($p < 0.05$), and by comparing pairs of modalities it is found that Touch failed more often before any of the other modalities than after (p for Pain < 0.001, for Cold < 0.01, and for Warm < 0.05). There are no other statistically significant relationships.

Summary of Results of Procaine Blocks.

The procaine results are given in Tables IV and V. The total

TABLE IV.—SENSORY DISSOCIATION IN ULNAR AREAS: PROCAINE BLOCKS

Site of stimulation	*Touch*	*Cold*	*Warm*	*Pain*
Area 1	19½	8½	12½	9½
Area 4	16	11	16½	6½
Area 6	14½	14	15½	6
Total	50	33½	44½	22

The figures are the sum of the individual ranks allotted to each modality as described in the text.

TABLE V.—SENSORY DISSOCIATION IN LATERAL POPLITEAL AREAS: PROCAINE BLOCKS

Site of stimulation	*Touch*	*Cold*	*Warm*	*Pain*
Area 1	7	10	14	9
Area 2	9½	9½	9	12
Area 3	7	11½	12½	9
Total	23½	31	35½	30

The figures are the sum of the individual ranks allotted to each modality as described in the text.

ranking order for the ulnar blocks is Pain, Cold, Warmth, Touch, in that order, and the data are just significantly concordant ($p<0.05$). For the lateral popliteal blocks the order of loss (Touch, Pain, Cold and Warm) is not the same, the rank not being significantly concordant. In both cases there is considerable inter-areal variation; thus in the ulnar blocks there is a gross difference between Cold and Touch in Area 1, but practically none in Area 6, and in the lateral popliteal blocks the relationship between Touch and Warm differs in Area 1 and Area 2. When the lateral popliteal results as a whole were compared with the ulnar results it was found that there was a statistically significant difference between the relationship of Touch to Pain in the two regions ($p < 0.01$). In consequence, it is probably not justifiable to combine the results for the two nerves and estimate the total rank; if, however, this is done, the coefficient of concordance falls far short of significance, as one would expect.

Comparison of Compression and Procaine Results.

Table VI summarizes the compression and procaine results. The mean rankings for procaine cannot be justifiably compared with the mean rankings for compression, since in no pair of rankings are both

TABLE VI.—COMPARATIVE DATA FROM COMPRESSION AND PROCAINE BLOCKS

I.—MEAN ORDER OF SENSORY LOSS

	Ulnar blocks (5 *subjects :* 15 *areas*)	*Lateral popliteal blocks* (4 *subjects :* 12 *areas*)	*Combined total* (9 *subjects :* 27 *areas*)
Pressure ..	Touch, cold, warm, pain (concordance not significant)	Touch, warm, cold, pain (concordance not significant)	Touch, cold, warm, pain (concordance significant: ($p<0.05$)
Procaine ..	Pain, cold, warm, touch (concordance significant : $p < 0.05$)	Touch, pain, cold, warm (concordance not significant)	Pain, cold, touch, warm (concordance not significant)

II.—STATISTICALLY SIGNIFICANT RELATIONS BETWEEN PAIRS OF MODALITIES

	Ulnar blocks (5 *subjects :* 15 *areas*)	*Lateral popliteal blocks* (4 *subjects :* 12 *areas*)	*Combined total* (9 *subjects :* 27 *areas*)
Pressure ..	Touch before pain ($p < 0.001$) Touch before warm ($p < 0.05$)	Touch before pain ($p < 0.01$) Touch before cold ($p < 0.01$)	Touch before pain ($p < 0.001$) Touch before cold ($p < 0.01$) Touch before warm ($p < 0.05$)
Procaine ..	Pain before touch ($p < 0.01$) Pain before warm ($p < 0.05$)		Pain before warm ($p < 0.01$)

significantly concordant. The figures given in the second part of the table show that in compression blocks the only relationships which have any statistical significance are those of the other modalities to Touch, while in the procaine blocks the only significant figures are those relating other modalities to Pain. It is clear from the table that in the ulnar blocks a statistically significant difference exists between procaine and compression blocks in respect of the relationship between Touch and Pain. By further comparisons of the raw data, additional information of this sort can be obtained. Thus in the ulnar blocks significant differences occur between compression and procaine with respect to the relationship between Touch and Pain ($p < 0{\cdot}001$), Pain and Warm ($p < 0{\cdot}01$) and Touch and Warm ($p < 0{\cdot}05$). In the lateral popliteal blocks no significant differences were found, but in the combined total different relationships hold between Touch and Pain ($p < 0{\cdot}001$), Pain and Warm (p $0{\cdot}001$) and Touch and Cold (p $0{\cdot}05$) in the two types of block.

It may thus be said that in this series statistically significant differences are demonstrable between the order of sensory loss in procaine block and the order in compression block, in spite of the dissociations being carried out on the same nerves in the same subjects under conditions in which all controllable factors (so far as they are known) capable of affecting the results were eliminated.

Discussion

A. *Order of Sensory Loss.*

We have summarized elsewhere (Sinclair and Hinshaw, 1950) the relevant literature on sensory dissociation by procaine and other local or spinal chemical anæsthetic agents, and have attributed the discrepancies between the results of different workers to the use of different (and sometimes unspecified) stimuli and end-points, differences in the exact area of skin tested, and neglect of individual variation.

The results obtained by previous workers on the dissociation produced by the application of pressure to a limb or to a nerve are set out in Table VII. There is much greater agreement than there is in the literature on chemical blocks, and those who have investigated compression blocks most fully (Boeri and di Silvestro, 1899; Lewis, Pickering and Rothschild, 1931; Lewis and Pochin, 1938) are all agreed on the order of sensory loss.

Nevertheless, we have found, as did Lewis and Pochin (1938), that the order of sensory loss in a given compression block can be varied by altering the characteristics of the stimulus. Such variability is, however, relatively small compared to the variability obtainable by this means in procaine blocks (Sinclair and Hinshaw, 1950). This is probably because the process of failure of a given modality is telescoped into a much

TABLE VII.—ORDER OF SENSORY PARALYSIS IN REGIONAL NERVE BLOCKS PRODUCED BY THE APPLICATION OF PRESSURE

Reference	*Number of* *Subjects*	*Blocks*	*Nerves Used*	*Method*	*Order of sensory loss* *Pain*	*Cold*	*Warm*	*Touch*	*Remarks*
Bastien and Vulpian, 1855	?	?	Sciatic, lateral popliteal, radial, median, ulnar	Direct pressure					Touch before pain
Herzen, 1886	1	?	Sciatic	Direct pressure					Cold before warm
Goldscheider, 1886	1	> 4	Radial	Direct pressure					Cold before warm and touch
Boeri and di Silvestro, 1899	Many	Many	Ulnar : sciatic	Compression cuff : direct pressure	4	2	3	1	
Fabritius and Bermann, 1913	?	?	Digital	Compression cuff					Touch before pain and temperature. Incidental observation
Hacker, 1914	> 1	?	Ulnar	Direct pressure	3=	1	3=	2	
Lewis Pickering and Rothschild, 1931	3	Many	Ulnar, median, radial	Compression cuff : direct pressure	4	2	3	1	
Zottermann, 1933	8	?	Ulnar	Compression cuff					Touch before pain
Clark, Hughes and Gasser, 1935	?	5	Ulnar, median, radial	Compression cuff	4	2	3	1	
Lewis and Pochin, 1938	?	?	Ulnar, median, —on dorsum of fingers	Compression cuff: direct pressure	4	2	3	1	Cold, warm and " first pain " almost simultaneously
Wortis, Stein and Joliffe, 1942	7	7	Medial and lateral popliteal	Compression cuff		2		1	Warm and pain never completely lost
Weddell, Sinclair and Feindel, 1948	6	Many	Ulnar, median	Compression cuff					Touch before pain. Incidental observation
Kellgren and McGowan, 1948	2	20	Ulnar	Direct pressure					Pressure before deep pain. Touch before cutaneous pain
Merrington and Nathan, 1949	2	?	Ulnar, median, radial	Compression cuff	4	3	1=	1=	

shorter time than in procaine blocks; thus the time between failure of touch to a No. 2 nylon thread and its failure to a No. 4 nylon thread may be only four minutes. If we then insist on a two minute gap between the failure of a pair of modalities before we record one as failing after another, it becomes almost impossible to alter the relationship of touch to another modality by altering the stimulus from a No. 2 to a No. 4 nylon thread. Variations in the stimuli and end-points used by different

writers will thus have less effect in altering the order of sensory loss than in procaine blocks, where the time factor is more lenient.

The second main cause of variability in the procaine blocks—differences in the response of different areas of skin—is also much less evident in compression blocks. Thus, in the present series of procaine blocks the order of loss in the hand was quite different from that in the leg, and in respect of the relation between Touch and Pain this difference was statistically significant. In the compression blocks, on the other hand, no statistical difference could be established between the results for the hand and those for the leg, and the ranking of the four modalities was much more nearly the same in the two situations.

The remaining major source of variation, from differences between subjects, appears to be equally important in both types of block. For example, in one subject Cold and Warm disappeared first in two of the three ulnar areas during the compression block (in all other areas in this series Touch was either first or first equal to disappear in compression blocks). In the same two areas of the same subject during procaine block Cold and Warm were also the first modalities to disappear. It will be noticed that in Table VII the number of subjects used in previous investigations is small—probably too small to reveal the extent of individual variation.

Several factors, therefore—the relative agreement in the literature, the relative uniformity of the overall results in the present series, and the relative difficulty of altering the apparent order of sensory loss by manipulating the experimental conditions—all combine to suggest that the order of sensory loss recorded in compression blocks is a more stable affair than it is in procaine blocks.

It appeared possible, on consideration of the procaine blocks alone, to sustain the view that the sensory dissociation produced might be entirely the result of factors other than the manner in which procaine attacks the nerve fibres. However, it has been shown that statistical differences are demonstrable between the results of procaine and compression blocks carried out under similar experimental conditions. It is clear, therefore, that if we consider the order of loss in procaine block to be an artefact residing in the experimental conditions, we cannot so regard the order of loss in compression block, and vice versa. If we are to maintain that the order of loss is an artefact in one type of block but not in the other, the evidence suggests that the procaine rather than the compression results should be regarded as the artificial ones. There remains, however, the possibility that in both types of block the order of loss is basically due to some regular influence, and that this influence can be upset to a greater or less extent by extraneous factors.

B. *Relation of Psycho-physiological to Electrophysiological Results*

No adequate explanation of the occurrence of sensory dissociation in compression and procaine blocks was put forward until 1929, when Gasser and Erlanger excised sensory nerves from frogs and mammals and exposed them *in vitro* either to pressure or to the action of cocaine. In general, the smaller fibres ceased to conduct before the larger fibres in cocaine block, while in pressure block the reverse was true. They emphasized, however, that this process was not always uniform, and that the order of increasing or decreasing size was not rigidly followed. This point has since been confirmed (Heinbecker, Bishop and O'Leary, 1934; Bishop and Heinbecker, 1935). The temptation to equate this general finding with the results of sensory dissociation experiments in the intact limbs of human volunteers was considerable, even though such a correlation necessitated the rejection of much recorded data on sensory dissociation which did not fit in. Indeed, the temptation was not always resisted (Ranson, 1931, 1933) and the idea is still prevalent that Touch is largely an affair of the biggest fibres and Pain an affair of the smallest, with temperature occupying a somewhat uncertain intermediate position.

However, no strict comparison can justifiably be made between the results in man and the work on excised nerve, owing to the numerous factors complicating the human experiments. The more important of these factors can conveniently be grouped as either Physical, Physiological or Psychological.

1. *Physical and Physiological*

The application of pressure to a nerve in the intact human body is a matter of considerable uncertainty. Irregular deformation is inevitable if the nerve is directly compressed against a rigid structure, and if a compression cuff is employed, animal experiments suggest that only a small and variable fraction of the pressure recorded in the cuff is actually transmitted to a nerve in the depths of the limb (Denny-Brown and Brenner 1944). Yet the result of dissociation experiments carried out by the two methods show fair agreement, suggesting that a common factor is involved. This factor is generally accepted to be asphyxia of the nerve trunk (Lewis, Pickering and Rothschild, 1931; Gasser, 1934; Weddell and Sinclair, 1947; Frankenhaueser, 1949; Causey and Palmer, 1949). The appropriate animal experiment with which to compare the human results would therefore seem to be one in which asphyxia rather than direct pressure is the blocking agent. Gasser (1943) has carried out such experiments on the intact animal, and has attempted to correlate his findings with the results of human sensory dissociation experiments. But Gasser (1934) has also reported experiments in which a cuff was inflated round the leg of an animal; the results of these experiments exhibit features in many ways

intermediate between the results of nerve compression *in vitro* (Gasser and Erlanger, 1929) and the results of asphyxia *in vivo* (Gasser, 1943). Cuff experiments would appear to be the most nearly comparable with compression blocks in man, but the number of such experiments is as yet too small (Gasser, 1950) to afford an adequate basis for comparison with the human results.

No attempt has been made as yet to duplicate in animals the physiological conditions obtaining in procaine blocks in man. In experiments on excised nerve the anæsthetic agent "soaks in" towards the centre of the nerve from all points on the circumference of the nerve, but in man a concentration gradient may exist across the nerve from side to side (Heinbecker, Bishop and O'Leary, 1934). It has not yet been established whether this difference would affect the electrophysiological results.

It is probable that to obtain an observable sensory dissociation by procaine block the procaine must be introduced around the nerve rather than into it. We have reported (Sinclair and Hinshaw, 1950) an ulnar procaine block in which all modalities of sensation were almost immediately lost, and we assume that this was due to the injection being made directly into the nerve trunk and not outside its epineurium. Kato (1936) considers that most of the time taken to establish blocking in experiments on excised nerve trunks is due to the process of penetration of the nerve sheath by the agent. *In vitro* this process is probably the passive one of diffusion, but in the intact nerve trunk in man circulatory function may play an important part, and the disposition of tissue fluid and blood vessels within the nerve trunk could then influence the way in which the individual fibres were exposed to the agent.

2. *Psychological*

Attempts to duplicate experiments on sensation in animals inevitably suffer from the disadvantage, on which Letiévant (1873) eloquently dilated, that no animal is capable of describing its sensations. Strictly, therefore, no correlation between the electrophysiological and the psycho-physiological approaches is possible unless man is used as the experimental animal (Jenkins and Stone, 1941), and perhaps the development of such techniques as that of Dawson and Scott (1949) may ultimately render this feasible (cf. Magladery McDougal and Stoll, 1950). Even this method, however, is open to objection in view of the number of factors—other than the specific effect of the agent on the nerve fibres—involved in any human experiment.

In both procaine and compression blocks there is little doubt that in a given area of skin the distribution of any one sensory modality appears to become diminished at random (Zotterman, 1933; Sinclair, 1948;

Weddell, Sinclair and Feindel, 1948), and it might appear plausible to assume that the agent affected all modalities at random, the modalities subserved by successively failing fibres being the concern only of chance. In this case we could ascribe the apparent failure of one modality before another to quantitative inequivalence of the sensory end-points adopted (cf. Cobb, 1919). The failure of any modality appears to be a continuous process. We have selected an arbitrary point in this process at which we have agreed to consider the modality to have failed, but we do not know that the point we have fixed for one modality is equivalent to the point we have fixed for another. Thus the end-point for touch may be reached when 80 per cent of the fibres mediating touch have failed, while the end-point for pain may be reached with a loss of only 50 per cent of the fibres mediating pain.

This conception could be extended to cover variations in the order of sensory loss in different areas of the same nerve territory. It is a matter of common experience that the density of tactile innervation is greater in the finger tip than in the palm. We have found that temperature sensibility is poorer in the finger tip than in the palm, and this suggests that temperature-conveying fibres are less numerous in the nerve supply of the finger tip than elsewhere. Much other evidence (Sinclair and Hinshaw, 1950) exists to show that the relative initial representation of each of the four modalities varies according to the area tested. If, then, fibres fall out at random irrespective of the modality which they subserve, the modality with the smallest initial representation in a given area will reach its end-point first. Thus we might conclude that the initial sensibility of the area tested has an effect in determining the order in which sensory loss in that area occurs. Such a concept would adequately explain, for a given agent, the variation between subject and subject, between one skin area and another, and between one testing method and another. Similarly, the greater density of innervation of hairs would explain the finding that both in compression blocks (Sinclair, 1948) and in procaine blocks (Sinclair and Hinshaw, 1950) hair touch persists longer than skin touch.

These assumptions, however, fail to explain the differences observed between procaine and compression blocks. We have compared the two types of block on the same subjects, using the same testing methods, the same skin areas and the same end-points: yet statistically significant differences can be demonstrated between the order of sensory loss in the two cases. We must therefore conclude that our original assumption was wrong, and that the order in which fibres cease to convey impulses is not solely a matter of chance. There must, in fact, be some form of selective action on the fibres in the sensory nerve. We do not know the nature of

this selective action—theoretically it could be due either to differences in the spatial distribution of the modalities throughout the nerve trunk (Barker, 1896), or to physical or chemical differences in the fibres themselves. There is little evidence to support the first concept, and the electrophysiological evidence is in favour of the second.

Let us then suppose that in the intact human being the fibres cease to function in an order roughly dependent on the basis of their size. Such a supposition alone will not explain all the experimental findings—for example it cannot explain differences in the order of sensory loss in procaine block according to the region tested. We could, however, by combining this assumption with our previous ones, interpret the differences between procaine and compression blocks in one of two ways: either the order of loss in both types of blocks is dictated by the size of the fibres conveying each modality, and the other factors we have mentioned interfere with this order to a greater or lesser extent, sometimes overriding it completely; or the order of loss is dictated in this way in one type of block but not in the other.

The relationship of fibre size to type of sensation conveyed has been the subject of much discussion (Adrian, 1932; Gasser, 1934, 1943, 1946). The electrophysiological results (Gasser, 1943) indicate a tendency for fibres to fail in the following order:

Procaine Block	*Asphyxial Block*
Unmyelinated fibres ("C" fibres)	Small myelinated fibres
Small myelinated fibres	Large myelinated fibres
Large myelinated fibres	Unmyelinated fibres ("C" fibres)

It is difficult to reconcile these findings with the results we have obtained in procaine and compression blocks in man (*see* Tables II, III, IV, V, and VI) but the attempt leads to the following conclusions:

(1) The initial sensibility of the area tested in part determines the order in which sensation fails in that area.

(2) "That the fibres belonging to different modalities must be widely distributed throughout the various fibre sizes, and that there seems to be little possibility of associating any one sensation with an elevation in the electroneurogram" (Gasser, 1943).

(3) That any one sensory modality is not evenly spread throughout the range of its fibre size distribution.

These conclusions account for the majority of the observations in sensory dissociation experiments. Certain findings, however, still remain to be explained. For example, as Gasser (1943) has pointed out, the time relationships of certain changes within the modalities of touch and pain in compression blocks are puzzling.

Evidence on the reaction time of pain and on the conduction velocity of nerve fibres indicates that some at least of the small myelinated fibres convey pain (Piéron, 1929; Adrian, 1932; Zotterman, 1939). In asphyxial and compression blocks in animals, this group fails before the largest myelinated group (Gasser, 1934, 1943), and it would therefore be expected that, in compression blocks in man, pain sensibility would show some signs of exhaustion at least with, if not before, the first manifestations of alterations in the modality of touch. This point has not yet been fully investigated, but Weddell, Sinclair and Feindel (1948) have noted that frequently changes in the quality of pain sensibility can be detected shortly before the disappearance of touch responses. Our own observations in the present series of compression blocks suggest that disturbances in the modalities of pain and temperature can often be detected much earlier than this. These early changes might be detected more frequently were it not for the relative difficulty of discrimination between pain or temperature sensations slightly altered in quality and intensity. Nevertheless, the *first* symptom in both procaine and compression blocks is invariably a subjective disturbance of the sensation of touch, which is also the last sensation to return to its fully normal subjective condition (cf. Kiesow, 1928). In order to explain this observation it is necessary to consider the implications of the subjective findings in sensory dissociation.

Clinical experience shows that even an extremely slight disturbance of the pattern of the impulses making up the familiar experience of touch is detectable subjectively. On the other hand, it is likely that the "yes or no" responses which we record in this type of investigation depend on the activity of a proportion of the large fibres, since it is probably the first part of the touch sensation complex which determines our recognition of whether or not we have been touched. The subsequent sensations arriving by slow fibres may merely serve to add "overtones" to the original experience, perhaps enabling us to determine the *kind* and *quality* of the touch (cf. Gasser, 1946). These considerations would account for the early loss of touch responses in compression blocks and their late persistence in procaine blocks, and at the same time explain the early subjective changes in the modality of touch in both cases.

Pain, on the other hand, is an experience only occasionally undergone, and it may be that a much larger disturbance among the fibres conveying it is necessary for the recognition that pain sensibility is disturbed. Furthermore, in the experience of pin-prick, the factor which determines whether the subject reports a feeling of pain or not is probably not the initial prick, conveyed by fast fibres, but what we may term "unpleasantness" which arrives subsequently by the slower fibres. Indeed, some authorities (Le Dantec, 1919; Piéron, 1923, 1929, 1930, and others) suggest

that the sensation of prick should not properly be considered as a true pain sensation. After the slow unpleasantness has been removed in procaine blocks, there is a period when it is exceedingly difficult to determine whether a pin-prick should be reported as "sharp" or as "sharp and painful." Thus we may suppose that in procaine blocks the early loss of the small fibres leads to an apparently early demise of the sum total of pain sensibility. In compression blocks there is indeed an early disturbance of function in the larger myelinated fibres conveying the sensation of prick, but this is not apprehended by the subject so long as the small fibres, which give him the response characteristically identified by him as "pain," are intact. In compression experiments pain begins to be subjectively disturbed at or about the time of failure of responses to touch. The continuing function of the smaller fibres is inadequate to produce a reaction to a touch stimulus of the type employed, while they are still capable of giving a very unpleasant sensory experience within the modality of pain (Weddell, Sinclair and Feindel, 1948). It is also to be expected that in compression blocks an unpleasant alteration of the quality of pain sensibility would be much more in evidence than in procaine blocks, and the prediction is borne out by observation.

Thus if we superimpose upon an admittedly variable order of blocking of the sensory fibres in the nerve various physical, physiological and psychological considerations, all dictated by the fact that the experiments are being done in an intact human subject, we can explain the apparent lack of correlation between the animal experiments and the human ones, and the gross variability of the latter in specific instances.

We have already concluded that in any fibre size group, more than one sensation must be represented. We must now add the conclusion that the distribution of physiological sensory function is not necessarily correlated with the distribution of psychological sensory function. It is unlikely that an exact correlation of sensation with fibre size will ever be made by the comparison of human sensory dissociation experiments with electrophysiological work, whether this be carried out on animal nerve or even in the conscious human subject.

Summary and Conclusions

The way in which sensation becomes lost in the sensory territories of the ulnar and lateral popliteal nerves during the development of a compression block of these nerves has been studied in 14 subjects. As in the case of procaine blocks, the order of sensory loss can be varied according to the precise skin area tested and the characteristics of the stimulus employed; there is also some individual variation.

In nine of the subjects a direct comparison has been made between

the results of sensory dissociation produced by procaine and compression blocks. Statistically significant differences are demonstrable between the order of sensory loss in the two types of block, in spite of the dissociations being carried out on the same nerves in the same subjects under standard conditions in which all controllable extraneous factors capable of affecting the result were eliminated. Such differences lead to the conclusion that in either or both types of block the order of sensory loss must be basically dictated by some factor connected with the type of agent used, and cannot be solely due to the operation of psychological factors; the most likely of such basic factors appears to be the elimination of the nerve fibres in an order which is a function of their size.

These findings have been discussed in regard to the relationship between experimental sensory dissociation in man and fibre dissociation in mammalian nerves. It is concluded that, in view of the multiplicity of physical, physiological and psychological factors involved in the human experiments, a correlation of this sort is not likely to be very fruitful. Nevertheless, there is nothing in the human results inconsistent with the view expressed by Gasser (1943) that each modality of sensation is widely distributed throughout the range of fibre sizes, provided it is accepted that such a wide distribution of physiological function does not necessarily imply psychological equivalence of all the sensations which can be produced by stimulation of fibres in a given size group.

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REFERENCES

ADRIAN, E. D. (1932) The Mechanism of Nervous Action, London, O.U.P.

BARKER, L. F. (1896) A case of circumscribed unilateral and elective sensory paralysis, *J. Exp. Med.*, **1**, 348.

BASTIEN, J-B., and VULPIAN, A. (1855) Mémoire sur les Effets de la Compression des Nerfs, *Gaz. Méd.*, p. 794.

BISHOP, G. H., and HEINBECKER, P. (1935) The afferent function of non-myelinated or C Fibers, *Am. J. Physiol.*, **114**, 179.

BOERI, G., and DI SILVESTRO, R. (1899) Sur le mode de se comporter des différentes sensibilités sous l'action de divers agents, *Arch. Ital. de Biol.*, **31**, 460.

CAUSEY, G., and PALMER, E. (1949) The effect of pressure on nerve conduction and nerve-fibre size, *J. Physiol.*, **109**, 220.

CLARK, D., HUGHES, J., and GASSER, H. S. (1935) Afferent function in the group of nerve fibers of slowest conduction velocity, *Am. J. Physiol.*, **114**, 69.

COBB, S. (1919) Cutaneous sensibility in cases of peripheral nerve injury; epicritic and protopathic hypothesis of Head untenable, *Arch. Neurol. Psych.*, **2**, 505.

DAWSON, G. D., and SCOTT, J. W. (1949) The recording of nerve action potentials through skin in man, *J. Neurol. Neurosurg. Psychiat.*, **12**, 259.

DENNY-BROWN, D., and BRENNER, C. (1944) Paralysis of nerves induced by direct pressure and by tourniquet, *Arch. Neurol. Psych.*, **51**, 1.

FABRITIUS, H., and VON BERMANN, E. (1913) Zur Kenntnis der Haut und Tiefensensibilität, untersucht mittels der Abschnurungsmethode, *Arch. f. Physiol.*, **151**, 125.

FRANKENHAUESER, B. (1949) Ischaemic paralysis of a uniform nerve, *Acta Physiol. Scand.*, **18**, 75.

—— (1933) Cutaneous sensation, *Science*, **78**, 395.

GASSER, H. S. (1934) Conduction in nerves in relation to fiber types, *Proc. Ass. Res. Nerv. Ment. Dis.*, **15**, 35.

—— (1943) Pain producing impulses in peripheral nerves, *Proc. Ass. Res. Nerv. Ment. Dis.*, **23**, 44.

—— (1946) Mammalian nerve fibers, Nobel Lecture 1945. Stockholm, Norstedt.

—— (1950) Personal communication.

——, and ERLANGER, J. (1929) The role of fiber size in the establishment of a nerve block by pressure or cocaine, *Am. J. Physiol.*, **88**, 581.

GOLDSCHEIDER, A. (1886) Zur Dualität des Temperatursinns, *Pflüger's Arch.*, **39**, 96.

HACKER, F. (1914) Versuche über die Schichtung der Nervenden in der Haut, *Zeit. f. Biol.*, **64**, 189.

HEINBECKER, P., BISHOP, G. H., and O'LEARY, J. (1934) Analysis of sensation in terms of the nerve impulse, *Arch. Neurol. Psych.*, **31**, 34.

HERZEN, A. (1886) Ueber die Spaltung des Temperatursinnes in zwei gesonderte Sinne, *Pflüger's Arch.*, **38**, 93.

JENKINS, W. L., and STONE, L. J. (1941) Recent research in cutaneous sensitivity: II Touch and the neural basis of the skin senses, *Psychol. Bull.*, **38**, 69.

KATO, G. (1936) On the excitation, conduction and narcotization of single nerve fibres, *Cold Spring Harb. Sym. Quant. Biol.*, **4**, 202.

KELLGREN, J. H., and MCGOWAN, A. J. (1948) On the behaviour of deep and cutaneous sensibility during nerve blocks, *Clin. Sci.*, **7**, 1.

KENDALL, M. G. (1945*a*) The Advanced Theory of Statistics. Volume I. London, Griffin.

—— (1945*b*) The treatment of ties in ranking problems, *Biometrika*, **33**, 239.

KIESOW, F. (1928) The problem of the condition of arousal of the pure sensation of cutaneous pain, *J. Gen. Psychol.*, **1**, 199.

LE DANTEC, A. (1919) Dissociation electro-physiologique de la sensibilité cutanée chez l'homme normal. Dissociation de la douleur chez les blessés de guerre. Traitement *Journal de Médicine de Bordeaux*, **90**, 451, 483.

LETIÉVANT, E. (1873) Traité des Sections Nerveuses. Paris, Baillière.

LEWIS, T., and POCHIN, E. E. (1938) Effects of asphyxia and pressure on sensory nerves of man, *Clin. Sci.*, **3**, 141.

——, PICKERING, G. W., and ROTHSCHILD, P. (1931) Centripetal paralysis arising out of arrested bloodflow to the limb, *Heart*, **16**, 1.

MAGLADERY, J. W., MCDOUGAL, D. B., and STOLL, J. (1950) Electrophysiological studies of nerve and reflex activity in normal man. II The effects of peripheral ischemia, *Bull. Johns Hopkins*, **86**, 291.

MERRINGTON, W. R., and NATHAN, P. W. (1949) A study of post-ischæmic paræsthesiæ, *J. Neurol. Neurosurg. Psych.*, **12**, 1.

PIÉRON, H. (1923) Comment se peut Concevoir la "Sensation" de Douleur, *Rev. générale des Sciences*, **34**, 365.

—— (1929) La Dissociation des Douleurs Cutanées et la Différenciation des Conducteurs Algiques, *L'Année Psychologique*, **30**, 1.

—— (1930) Temps de Réaction et Dissociation des Douleurs Cutanées, *C.R. Soc. de Biol.*, **103**, 883.

RANSON, S. W. (1931) Cutaneous sensory fibers and sensory conduction, *Arch. Neurol. Psych.*, **26**, 1122.

RANSON, S. W. (1933) Cutaneous sensation, *Science*, **78**, 395.

SINCLAIR, D. C. (1948) Observations on sensory paralysis produced by compression of a human limb, *J. Neurophysiol.*, **11**, 75.

——, and HINSHAW, J. R. (1950) Sensory changes in procaine nerve block. *Brain*, **73**, 224.

WEBER, E. M. (1847) Ueber der Einfluss der Erwärmung und Erkaltung der Nerven auf ihr Leitungsvermögen Müller's Arch, p. 342.

WEDDELL, G., SINCLAIR, D. C., and FEINDEL, W. H. (1948) An anatomical basis for alterations in quality of pain sensibility, *J. Neurophysiol.*, **11**, 99.

——, —— (1947) Pins and needles: observations on some of the sensations aroused in a limb by the application of pressure, *J. Neurol. Neurosurg. Psychiat.*, **10**, 26.

WORTIS, H., STEIN, M. H., and JOLIFFE, N. (1942) Fibre dissociation in peripheral neuropathy, *Arch. Int. Med.*, **69**, 222.

ZOTTERMAN, Y. (1933) Studies in the peripheral nervous mechanism of pain, *Acta Medica Scand.*, **80**, 185.

—— (1939) Nervous mechanism of touch and pain, *Acta Psychiat. et Neurol.*, **14**, 91.

SYMPTOMATIC "CATAPLEXY" OR CHALASTIC FITS IN CORTICAL LESION OF THE FRONTAL LOBE

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It is well-established that so-called cataplectic attacks may occur in lesions confined to diencephalic structures and the mesencephalon. Usually there are additional narcoleptic symptoms, but cataplexy occasionally occurs alone. Attacks of general limpness may be observed in infratentorial tumours. Apart from the absence of emotional precipitation they may be indistinguishable from those seen in cataplexy. It is assumed that they develop upon the tentorial herniation of the brain-stem, more particularly the mesencephalon, following a rise in intracranial pressure.

It seems to be more rare for accesses of general limpness or transient losses of muscular tone to occur in lesions affecting exclusively the cerebral cortex. On other occasions the present writer, however, has drawn attention to occurrence of "cataplectic" attacks in cortical lesions, affecting the mesial surface of both frontal lobes. These were all instances of intracranial tumour (1949, 1950). Recently two cases of depressed fracture over the lateral surface of the frontal lobe came under the observation of the author. They probably bear on the problem of so-called cataplectic attacks in cortical lesions.

Case 1 (AKH–G–6490).—A man of 25 received an injury of the head ten weeks before admission to this clinic. While harrowing he fell down. He was unable to recollect whether he stumbled or felt dizzy. Consciousness was lost for a short period of time. On coming to he was lying between the harrow and the horses, bleeding from a wound in the left frontal region. He vomited once or twice and had transient pains in the right ear. Although he felt a little dizzy he could walk home to the farm house. He did not stay in bed and his doctor was not sent for. He resumed activity after some hours. There was no weakness either of the face, arm or leg. After injury he complained of left frontal headache localized to, and just below, the wound. A few days after wounding accesses of general muscular limpness began to occur. These lasted from a few seconds to about half a minute, recurring from two to six times a day. The attacks occurred only when he was standing or walking. He sagged at the knees and occasionally sank down. He was usually awake and completely aware of his surroundings; only once did he feel a little sleepy, and a mild clouding of consciousness supervened. During attacks he never uttered a sound and though unable to recollect for certain whether he tried, he was inclined to think that he could not speak when attempting to. He knew nothing of eliciting factors. The attacks were never precipitated by strong emotions. On account of headache and these "hypotonic fits" he was admitted to the medical department of his County Hospital, from whence he came under observation in this clinic on June 4, 1949.

The patient was a healthy looking person of "lanky" build. He was well oriented and completely awake. He co-operated well but was a little retarded intellectually. Though originally left-handed he was now able to use both hands equally well. Neurological, ophthalmological and otological examinations did not reveal any abnormalities. On general physical examination the only abnormality noted was a scar in the left frontal region, where a circular, slightly depressed fracture, 2·5 cm. in diameter, was distinctly palpable. The depression of the bone was confirmed by radiograms of the skull. Electroencephalograms were not made and the cerebrospinal fluid not examined.

The patient was operated upon on June 6, 1949. Under local anæsthesia an incision was made, circumscribing the posterior two-thirds of the fracture. A craniotomy was performed around the fracture and the bone removed. On the inner surface of the bone a comminuted, partly healed fracture was found, conical in shape and depressed about 1·5 cm. in depth. There was no perforation of the dura, but an impression was made upon it by the bone. On reflecting the dura a corresponding impression was found upon the surface of the brain 1·5 cm. in depth. There was no cerebral laceration. During operation the cortical impression gradually disappeared, and the surface of the brain appeared normal. The depressed part of the bone was removed and the remainder replaced. The patient made a rapid recovery without incident and was discharged on the ninth day after operation. A dosage of phenobarbitone was administered. Six months after operation he reported complete relief from headache and attacks of limpness. He resumed activity as a farm hand one week after discharge and has continued in employment since. He is still on a regular dosage of phenobarbitone.

Case 2 (AKH–G–6506).—A girl of 14 had been kicked by a horse at the age of 8, sustaining a depressed fracture in the right frontal region. She was unconscious for a short period of time and detained in hospital for about six weeks. She was not submitted to surgical treatment. Since then she had complained of an occasional headache of variable intensity. Heat and mental efforts were aggravating factors. On occasion she experienced spells of dizziness and she had noticed an increasing tendency to irritability. During the two years before admission she had had a series of short attacks, lasting from one up to six to ten seconds. These were (*a*) sudden attacks of unconsciousness without warning, during which she fell down, (*b*) accesses of general limpness or muscular relaxation associated with blunting of consciousness to a varying degree, and, finally, (*c*) attacks during which consciousness was unimpaired; she went limp, sagged at the knees or sank down, though occasionally she was able to sit down. She was fully aware of what happened around her. The limpness affected more particularly the lower limbs; the arms were possibly also involved, but she had never dropped objects from her hands. During attacks she had never spoken nor uttered a sound, and on one occasion, she recollected, her attempt to speak was met with a complete failure. These three types of attack always occurred unassociated with the spells of giddiness mentioned above and were said, by the patient, to be of quite another nature. The accesses of limpness alone and those with an additional impairment of consciousness appeared irregularly both as regards intervals and sequence, at first once or twice a month, later with increasing frequency up to several times a day. There were no eliciting factors such as strong emotions and physical exertions.

The patient was a small, slenderly built girl of pale complexion. She was well oriented and alert. Intellectual powers were good. Retention—recall and attention tests were performed satisfactorily. Apart from an almost complete lack of all tendon reflexes no abnormalities were disclosed on neurological examination. Ophthalmological and otological examinations were normal. Lumbar puncture did not reveal any pressure disturbances. The spinal fluid contained protein in normal concentration and showed a mild increase in cellular elements. In the

right frontal region there was a slightly depressed scar circumscribed by a distinctly palpable, almost circular, bone edge. A depressed fracture about 2 cm. in diameter was disclosed in the radiograms of the skull. Electroencephalography and pneumoencephalography did not reveal any abnormalities. On June 16, 1949, a craniotomy was performed under local anæsthesia. A boneflap with a depressed fracture was reflected. The depression was about 2 cm. in depth and the fracture was completely healed. The bone protrusion made a conical impression upon the dura, but no

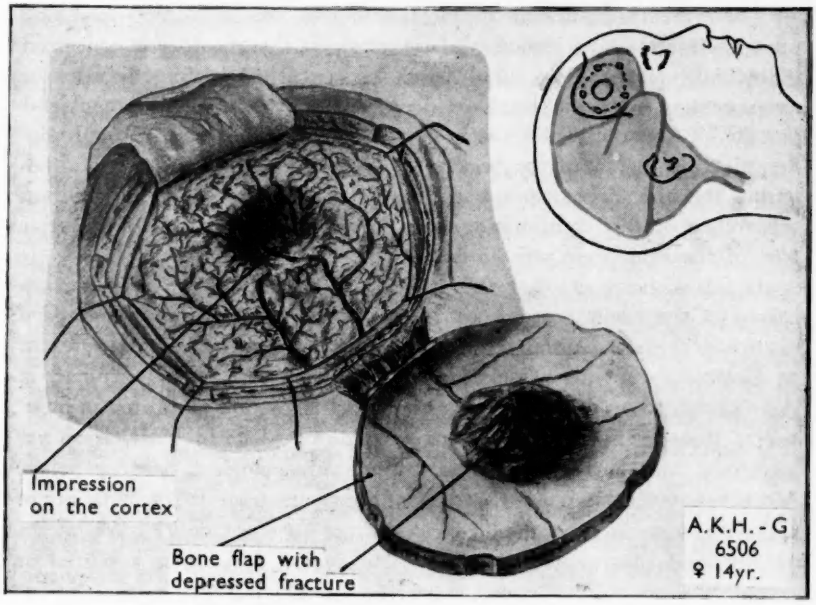

FIG. 1.

perforation was found (cf. fig. 1). On opening the dura a corresponding impression was disclosed on the surface of the brain. There were no adhesions between the dura, the arachnoid and the brain and no visible cicatrization of the cortex. As with Case 1 the cerebral tissue gradually slipped back during operation so as to make the appearance of the brain surface normal upon closure of the dura. The protruding portion of the fracture was removed and the boneflap replaced. There was primary union of the wound. The postoperative course was uneventful. On the seventh day after operation she was transferred to her County Hospital, which she was permitted to leave one week later. Five and a half months after operation she reported that all went well. There was a complete relief from headache, dizziness and accesses of limpness. She was still on a regular dosage of phenobarbitone of 1·5 gr. twice a day.

To sum up the main features of both cases described there is first of all the occurrence of paroxysmal phenomena, namely the rapidly transient accesses of general limpness. The attacks are usually unassociated with impairment of consciousness; in some instances clouding may develop, sometimes increasing to complete unconsciousness. There are

"negative" features such as the absence of narcoleptic traits and of emotional precipitation; also there are the facts that the lesion was of limited extension, affecting the cortex only, and that its localization could be ascertained with some degree of accuracy.

What is the "mechanism" of these attacks of limpness or rather what is their pathophysiological correlate?

There are two different approaches to this problem. We may look upon these attacks as instances of cataplexy as this disorder is conceived of by Adie (1926). We should then be concerned with a disorder of sleep, namely a specific, localized sleep of the "centres of movement and posture." Apparently Adie arrived at this conception of a pathophysiological basis for cataplexy because of the common coexistence of idiopathic or rather cryptogenic narcolepsy and cataplexy, and the common occurrence of this combination even in verified lesions of the anterior part of the brain-stem structures.

It seems, however, that the case is different when, in strict surface lesions of the brain, "cataplectic" attacks occur without additional sleep disturbances in the usual sense of that term. Apart from the attempt at localizing function which is implicit, when not indeed explicit, in Adie's conception, there is the question whether we are permitted to interpret a disorder in terms of sleep; a condition that, in itself, is as yet undefined and lacks explanation from a physiological point of view. Moreover, when sleep or disorders of sleep are used in explanation of these phenomena, why then restrict its use to these only? We might readily, and consistently with this view, regard aphasia as a partial or complete sleep of the "speech centre," etc. Obviously the implications of Adie's view are far-reaching, too far-reaching, so far as I am aware, since the majority of disorders encountered in clinical neurology might be interpreted in that way, and the remainder in terms of vigilance.

Another approach to the matter has been made by Kinnier Wilson (1940). He took the view that cataplectic phenomena result from abnormal impulses, inhibiting the activity of the nerve cells in the so-called motor cortex. Consequently attacks of cataplexy, or general limpness, may be classified as one of the epilepsies, namely as "inhibitory epileptic attacks." Impairment of consciousness may upon this view vary in proportion to the spread of abnormal impulses over the cortex.

Let us inquire a little further into the matter from this angle, since recent experimental researches have again brought to light the problem of "inhibition" and "suppression." When these results are interpreted cautiously I think they may prove of importance for our conception of the genesis of the attacks we are considering.

Perhaps it would not be amiss to recall in advance that information

gained from experiments on animals and man may not be assumed to mirror "normal" activities. Experimental stimulations of the cortex—be they electrical, chemical or mechanical—have nothing more to do with normal conditions than have pathological irritative and destructive processes. If any direct comparison were to be made, it would, other things being equal, be more permissible between experimental and pathological conditions, than between experimental and normal ones.

Bubnoff and Heidenhain (1881) reported that under varying experimental conditions both abnormal movements and the "reversed" condition, namely absence or "inhibition" of movement could be elicited from the same point of stimulation. This was corroborated by Brown and Sherrington (1912) who found that, under cortical stimulation, inhibition of movement was a phenomenon of outstanding prominence, even more than excitation itself and that it occurred more frequently alone. The work of Dusser de Barenne, McCulloch and collaborators (for reference cf. McCulloch, 1944) again demonstrated, in the monkey, the occurrence of relaxation of existing muscular tension. Besides this they also described a restraining of the excitability of the motor cortex outside the point stimulated. This they called "suppression," and I shall refer to it in the following as "suppression in the narrow sense." They claimed that both phenomena were elicited by stimulation of certain cortical areas only, which were termed "suppressor bands." An attempt has been made to identify the "suppressor areas" with certain architectonic fields. As far as the frontal lobe is concerned Dusser de Barenne and McCulloch identified the posterior "suppressor area" with Hines's (1936) so-called strip-zone, later 4s. In 1944 von Bonin described a corresponding specific architectonic organization of that field. McCulloch (1944) identified the anterior frontal "suppressor area" with area 8, which was assumed to be more extensive than originally described by Brodmann, and the mesial frontal "suppressor area" with area 24 of Brodmann, the anterior limbic area. It should be said, however, that the anatomical basis for these minute parcellations of the cortex, in the monkey, has been subjected to severe criticism by Lashley and Clark (1946). Later von Bonin, together with Bailey (1948), was more reserved. Although, in these writers' architectonic map of the macaque, the parcellation is still elaborate, the "suppressor areas" 4s and 2, at least, have disappeared. As for the results obtained under cortical stimulation in experimental animals there is no unanimity. The "functional" specificity of the "suppressor bands" have been questioned by several investigators. Tower and Hines (1935) and Hines (1937) were able to elicit relaxation of muscular tone not only by stimulation of the anterior part of area 4 but also of area 6. This latter observation is usually left unnoticed by those advocating the reality of

the "suppressor bands," as has been pointed out by Clark (1949). Tower (1936) and Clark and J. W. Ward (1948) also stimulated the motor cortex and noted relaxation of existing muscular tone. This was demonstrated in anæsthetized cats by the former writer and in unanæsthetized monkeys by the latter. Weak stimulation, that is to say stimulation below the threshold for motor response, was used in both cases. An increase of the intensity of the stimulus of such a point induced movement. Relaxation of tone was evoked both from the anterior and middle parts of the entire motor cortex. Relaxation of tone of the contralateral arm only was observed under stimulation of the postcentral gyrus by Clark and Ward (loc. cit.). These writers emphasize that this "inhibition of tone" must not be confused with "suppression" in the narrow sense of McCulloch and Ward. They incline to conceive of it as comparable to cortical reciprocal innervation and co-innervation. Finally, as for the mesial frontal surface, there are also discrepancies. While Smith (1945) and A. A. Ward (1948) demonstrated, in the anæsthetized monkey, profound relaxation of existing muscular tension and suppression of the neuronal activity of the remainder of the motor cortex upon stimulation of the anterior limbic area, Clark, Chow, Gillaspy and Klotz (1949) report convulsions ensuing upon a similar procedure in unanæsthetized dogs. When, on the other hand, the animal, which in the unanæsthetized state had yielded response of movement, was stimulated under light anæsthesia suppression of the excitability of the motor cortex and cessation of movement were noted. There is one report, available in abstract only (J. W. Ward, 1948) on "arrest of movement" ensuing, in the unanæsthetized cat, upon stimulation of the white matter of the cingulate gyrus. During stimulation the animal remained standing with one foreleg poised off the table, but no limpness was noted. Of the descending pathways involved in these abnormal processes we know very little. The basal ganglia do not seem to play a rôle. A. A. Ward (1948), using the degeneration method, found pathways from the anterior limbic region to the reticular formation in the mesencephalon. Whether they are of interest for the conduction of abnormal inhibitory impulses seems to be doubtful.

Although opinions differ as to the nature of the pathophysiological processes at work, there remains as a main point the fact that, under certain, varying experimental conditions, relaxation of muscular tone may be elicited on "irritation" of cortical areas. These seem not to be localized at random in the cortex. To maintain, however, the exclusiveness of the "suppressor bands" both as regards their localization and their "function" seems to be unwarranted for the present time. The cortical areas of interest are the entire "motor cortex" and the remainder of the mesial surface of the frontal lobe.

As for the localization of the lesion in the present cases of human pathology there is some degree of precision. In both cases recorded above the cerebral lesion was almost circular, about 2 cm. in diameter, located in the middle of the lateral surface of the frontal lobe, affecting the anterior part of the motor cortex, schematically represented in fig. 2. In a partly extracerebral oligodendroglioma of comparatively limited extension, in an ethmoidal meningioma and a meningioma of the falx, to which reference has been made in the initial paragraph, similar accesses of general limpness were related by the patients. The cortical

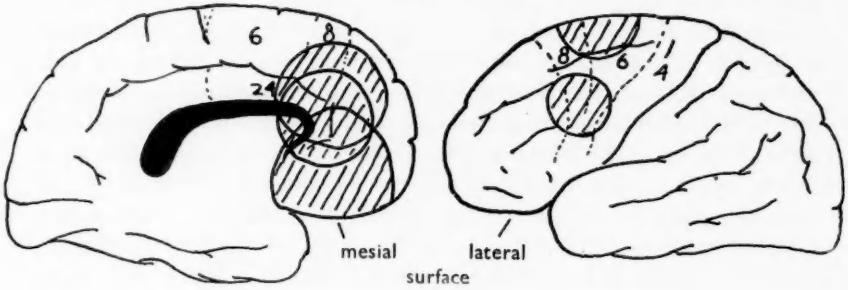

FIG. 2.

lesion was in all these cases confined bilaterally to the anterior limbic area and the neighbouring parts of the cortex, that is to say also the lower, mesial, anterior part of the motor cortex, and in the case of the ethmoidal meningioma an additional posterior three-fourths of the gyrus rectus bilaterally (cf. fig. 2). A corresponding part of the mesio-basal frontal cortex may be assumed to be affected in a case of ethmoidal meningioma, leading to attacks of general limpness, that has been reported by David and Askenasy (1937). These writers did not, however, emphasize the "cataplectic" nature of the attacks. Lund (1950) has described a case of parasagittal meningioma, of the size of a walnut, affecting the anterior part of the motor cortex (areas 6 and 8 grossly), in which no rise in intracranial pressure was disclosed. For five years before operation the patient had had attacks of loss of muscular tone. The attacks occurred only when he was standing or walking; that is to say that the standing tone was especially affected, as was the case with all the patients mentioned above. In Lund's case the attacks were never associated with clouding or loss of consciousness. Lund has also described accesses of general limpness in a certain group of mesio-temporal intracerebral tumours. Whether in these cases we are concerned with instances of true cortical affection is doubtful. It must be recalled that tumours of that location are apt, through tentorial herniation of the mesial part

of the temporal lobe, to affect indirectly the brain-stem at the level of the mesencephalon.

Thus, in the few instances of cortical traumatic lesion and extracerebral tumour, hitherto recorded, the areas affected coincide grossly with those parts of the cortex that, under stimulation in experimental animals, have yielded relaxation of muscular tone.

As for the nature of the lesion there is the question how it may lead to "irritative" phenomena. Common to extracerebral tumours and the cases of depressed fracture is the fact that a firm and in some instances irregular protrusion makes an impression upon the surface of the brain. While the protrusion, by being fixed directly or indirectly to osseous structures, is "immovable," the brain remains to some extent movable within the subarachnoidal space. Thus there are present the conditions for the development of traumata to the brain and the walls of the small cortical vessels. The difficulties in deciding upon either of these as a causal agent are apparent. I think, however, that the former is less probable, since, in extracerebral meningioma, there is no interrelation between the size of the tumour and the onset of symptoms. It is not rare for a meningioma to make a definite impression upon the cortex for many years without eliciting symptoms. This seems to suggest that a vascular component is the necessary condition for irritative signs to occur. There are some observations that tend to support the view that we are concerned with impediment of arterial circulation rather than with venous obstruction. Histological examination of the cortex immediately adjacent to extracerebral meningiomas and of that in the oligodendroglioma recorded by the present writer revealed a varying degree of atrophy of the neuronal elements; in some instances there was an additional proliferation of the glia and a definite decrease in number of the small arteries and capillaries. This is the histological picture, that, by Alexander and Putnam (1938), has been considered the pathological correlate of partial arterial obstruction and, consequently, of inadequate oxygen supply. It is reasonable, I think, to believe that intermittent diminution of the arterial circulation may ensue upon spasm of the small cortical arteries, spasm elicited by mechanical stimulation.

In the cases of depressed fracture, in which no histological examination has been performed and in which neither atrophy nor contusion were noted during operation, an identical process may have been at work, but its nature naturally remains a matter of conjecture. The assumption, however, that these lesions may, at times, lead to "weak irritation" does not seem unreasonable. Not only are they "mild," but they occurred in young persons in whom the possibilities for a rapid compensation for failing circulation and oxygen supply are well developed.

The sequence of pathophysiological events that, at the present time, is thought to underlie the usual focal epileptic attack may be summed up as follows. A circumscribed area of the cortex may, through transient arterial spasms, be affected in such a way that, at a given time, oxygen supply is inadequate to maintain normal metabolism and hypoxic metabolism of the nerve cells supervenes. At a certain stage of ischæmia abnormal impulses are discharged from the affected cells. At first the abnormal "uncontrolled" discharges are conveyed along pre-existing pathways; but when self-sustaining discharges occur they may come to "fire" contiguous areas, irrespective of cortico-subcortical connexions, and eventually the entire cortex and subcortex may become involved in the process, until the cells are "exhausted," that is to say depleted of energy stored in phosphate bonds, and their activity hampered by increasing acidity of the tissue. The experimental evidence has among others been supplied by Bronk (1938), Penfield and collaborators (1939, 1940, 1941), McCulloch (1944) and Ward, McCulloch and Kopeloff (1948). In the case of partial or total involvement of the cortex and subcortex, clouding of consciousness or complete unconsciousness respectively develop.

If, in affections of the motor cortex, the neuronal irritation is "weak" the "reversed" condition of the usual local or generalized epileptic fit may ensue, that is to say general limpness or loss of existing muscular tone and inability to move. The abnormal discharges are probably mediated via connecting pathways to the lower brain-stem in the first instance. This sequence of events may be assumed to underlie the attacks of general limpness in the present two cases of depressed fracture and in Lund's case of parasagittal meningioma of limited extension. There has been no need, so far, of either minute areas within or suppression of neuronal activity of the motor cortex.

The case is somewhat different when lesions of the mesial frontal cortex are to be considered. Firstly, the present mesial cases differ from those of the convexity and the parasagittal region in that they involve extensive cortical areas, including the lower anterior mesial motor cortex unilaterally and the anterior part of the cingulate gyrus bilaterally. Secondly, the results of stimulation in experimental animals have not yielded conclusive evidence for or against the occurrence of relaxation of tone and of suppression in the narrow sense. In unanæsthetized animals convulsions were evoked by stimulation of the anterior limbic area. Only once has "arrest of movement" been noted. Suppression has only been demonstrated, for certain, in anæsthetized animals. May "arrest of movement" and "suppression of neuronal activity" be taken not only as different aspects but also as varying degrees of the same process?

We are unable, I think, to answer this question for the present; but an answer in the affirmative cannot be precluded. Further, may circulatory changes within extensive areas of both frontal lobes be assumed to lead to a state comparable, in a way, to that of light anæsthesia? There are certain observations that may bear on this question. Tower (1936) and Tower and Hines (1944) found that, after interference with cerebral circulation and under anæsthesia, the relative degree of elicitability of relaxation of muscular tone and movement was changed in favour of the former. This seemed to be brought about by an increase in threshold values for responses of movement. As for the anæsthetized state this is in agreement with Clark and collaborators' observations (1949). Thus, neuronal dysfunction of extensive cerebral areas together with intermittent states of irritation of the anterior part of the cingulate gyrus would seem to be the requirements for accesses of general limpness to occur in mesial frontal lesions. We should, consequently, be concerned with an instance of suppression, that is to say a restraining or arresting of the activity of the neurones in the remainder of the motor cortex, as has been suggested by Kinnier Wilson, but not in the narrow sense of Dusser de Barenne, McCulloch and Ward. There is no reason for considering suppression, as described above, a specific (abnormal) function of the anterior limbic area when stimulation, in isolation, of that area is at most a necessary but not a sufficient condition for the occurrence of limpness. Whether pathways, such as those described by A. A. Ward, from the anterior limbic area to the reticular formation of the mesencephalon may play a part in the conduction of "inhibitory impulses" we do not know for certain. It is, however, rendered less probable by the fact that there is no agreement between the results of experimental "isolated" stimulation of the motor cortex and the anterior limbic area. Finally, it must be recalled that the anterior lower mesial motor cortex was also affected in the present mesial tumours, and this region cannot be excluded as a site of relevant irritation.

So far there has been paid no attention to disorders of consciousness. In some instances blunting or loss of consciousness occurred. These were reported both in "mild" limited and in extensive lesions. In the usual focal epileptic attacks disorders of consciousness are assumed to vary as the spread of "uncontrolled" discharges when these latter increase in intensity. As for the present cases there are, obviously, difficulties in this explanation, so far, at least, as "mild" lesions of the anterior motor cortex are concerned. In unanæsthetized animals an increase in intensity of the stimulus changed the response from relaxation of tone to movements or convulsions. How are we to account for the absence of convulsions in these accesses of general limpness when associated with disorders

of consciousness? The solution of this problem is possibly bound up with the difference between experimental and pathological conditions. Although in the cases of depressed fracture the lesions are of limited extension they must nevertheless be regarded as extensive as compared with the point stimulation under experimental circumstances. Also there is the assumption that changes in cellular activity ensue upon circulatory changes, so that the above observation by Tower and Hines may be relative to the discussion. In his explanation of sudden and rapidly transient unconsciousness in circulatory disorders of the brain Cobb (1948) assumes as the remaining possibility that a sudden spread from a local ischæmic zone of abnormal discharges occur, completely "blotting out" consciousness. Under these circumstances convulsions do not usually occur. Whether we are concerned with suppression that, besides to irritation, may be ascribed to additional causes we cannot tell. On the other hand, it would not for the present seem justified to assume a difference, in principle, between the pathophysiological processes underlying disorders of consciousness in the usual focal epileptic attacks and those in the present cases.

There remains to be considered the question of "generalization" of the accesses of limpness or chalastic fits. All the cases referred to in this paper had bilateral loss of tone, especially affecting both lower limbs. This was so whether the lesion was bilateral or unilateral. This feature should not detain us were it not for the fact that cortical lesions elsewhere located seem to lead to localized attacks of limpness. This question has already been touched upon by Whitty (1947) and the present writer (1950). Localized accesses of limpness, involving, for instance, the contralateral upper limb, have not, so far as I am aware, been observed in lesions confined exclusively to the frontal lobe. The areas affected have been the pre- and postcentral regions and the parietal lobe parasagittally. Besides the frontal and temporal lobes this latter region was also affected in Whitty's cases. Whether there is a difference between the "central-parietal chalasis" and the "frontal one" is open to debate. There is, however, a similarity between these clinical cases and Clark and Ward's observations in experimental animals (1948), though it may be superficial. On the other hand, we are not permitted to draw a parallel between the "generalizing" of the attacks of limpness and that of the usual focal epileptic attack, elicited by lesion of the anterior part of the motor cortex. It is true that unilateral cortical lesions of that location are more apt, probably via numerous so-called homoiotopic commissural fibres, to lead to generalization of the epileptic fit than are those located farther backwards in the "motor area proper." But there are no experi-

mental results, suggesting the existence of similar commissural fibres so far as inhibitory or chalastic impulses are concerned.

Although accesses of symptomatic "cataplexy" or general limpness differ from the usual focal epileptic attacks both as regards their gross phenomenology and some of the underlying pathophysiological processes it seems reasonable to consider them one of the epilepsies. But the appropriateness of the term "inhibitory" epilepsy is more doubtful. I think it will be well to consider this in conjunction with some remarks on the nomenclature. An ample choice of terms has been used to describe the attacks we are considering. They have varyingly been termed symptomatic "cataplexy," accesses of general limpness, hypotonic attacks, transient losses of muscular tone and attacks of muscular relaxation. Terms such as "inhibitory epilepsy" and the possible "suppressor epilepsy" have been avoided. The multivocality of the term "inhibition" renders it a little difficult to handle in clinical neurology. Does it cover the relaxation of tone only or may we include the arrest of movement? Do we mean a physiological process comparable to reciprocal innervation? Are we concerned with "inhibition of tonic innervation"? The matter becomes even more complicated when the subdivisional concept of suppression is introduced. In the sense of arresting or restraining the activity of the nerve cells in the motor cortex this term has been used vaguely by Kinnier Wilson, too narrowly, as it seems, by Dusser de Barenne, McCulloch and A. A. Ward and, finally, under certain definite circumstances only by Clark and co-workers. Many of these questions are still open to debate. The term "chalastic fit" has only a few times appeared among the already copious number of descriptive terms. It is, however, this term I shall propose to denote the attacks of limpness. The term "chalasis" is of ancient usage in medicine. After a period of disuse it has recently been revived by Hines and Boynton (1940) in the sense followed here. Chalasis simply means relaxation of the weak parts of the body. Thus it is only descriptive and non-committal. It has been preferred to the term "relaxation" since the latter is ambiguous and has, moreover, been used in other fields of medicine with certain connotations distinct from the present one. Finally, as for the term "cataplexy," it must be considered infelicitous in this connexion, since the Greek word "cataplexis" means dismay, dread, apprehension and consternation. Thus cataplexy implies an emotional precipitation which has not been disclosed in the present cases. There is possibly no difference, in essence, between cataplexy and chalastic fits, when the former occurs in lesion of the anterior part of the brain-stem and neighbouring part of the brain. In that case there may be involvement of pathways from the frontal cortex to the mesencephalon and the pons.

SUMMARY

Two cases of depressed fracture are described, making an impression upon the lateral surface of the frontal lobe corresponding to the anterior part of the motor cortex (Areas 8 and 6). So-called cataplectic attacks or accesses of general limpness developed in both cases, sometimes associated with blunting or loss of consciousness. The few cases on record of extra-cerebral tumour affecting the cortex exclusively, in which similar accesses have been described, are briefly reviewed. In some instances the cortical areas involved were those mentioned above, in others the mesial frontal cortex bilaterally, including the anterior limbic area and the lower mesial part of the motor cortex. The genesis and the pathophysiology of the attack of limpness are considered in the light of recent experimental investigations. It is taken to be one of the epilepsies. Although the term "inhibitory epilepsy" has been used to describe the attacks under consideration, its appropriateness seems for the present to be a little doubtful. The term "chalastic fit," therefore, has been proposed to denote attacks of symptomatic "cataplexy" or general limpness, since this term is only descriptive and non-committal.

REFERENCES

ADIE, W. J. (1926) *Brain*, **49**, 257.

ALEXANDER, L., and PUTNAM, T. (1938) *Proc. Ass. Res. Nerv. a. Ment. Dis.*, **18**, 471.

BONIN, G. VON (1944) Chapter II in Bucy, P. C.: The Precentral Motor Cortex, Urb., Ill.

——, and BAILEY, P. (1948) The Neocortex of the Macaca Mulatta, Univ. Ill. Press, Urb., Ill.

BRONK, D. W. (1938) *Proc. Ass. Res. Nerv. a. Ment. Dis.*, **18**, 298.

BROWN, T. G., and SHERRINGTON, C. S. (1912) *Proc. Roy. Soc. Lond. Ser. B.*, **85**, 250.

BUBNOFF, N., and HEIDENHAIN, R. (1881) *Arch. f. d. ges. Physiol.*, **26**, 137.

CLARK, G. (1949) *The Quarterly—The Chicago Med. School.*, **10**, 14.

——, CHOW, K. L., GILLASPY, C. C., and KLOTZ, D. A. (1949) *J. Neurophysiol.*, **12**, 459.

——, and WARD, J. W. (1948) *Brain*, **71**, 332.

DAVID, M. V., and ASKENASY, H. (1937) *Rev. neurol.*, **68**, 489.

ETHELBERG, S. (1949) *Acta Psychiat. et Neurol.*, **24**, 421.

—— (1950) On the Anterior Cerebral Artery. A Clinical and Angiographic Study of Its Circulatory changes. (To be published.)

HINES, M. (1936) *Am. J. Physiol.*, **116**, 76.

—— (1937) *Bull. Johns Hopkins Hosp.*, **60**, 313.

——, and BOYNTON, E. P. (1940) *Contrib. Embryol. Carnegie Inst.*, **28**, 309.

LASHLEY, K. S., and CLARK, G. (1946) *J. Comp. Neurol.*, **85**, 223.

LUND, M. (1950) On Epilepsy in Intracranial Tumours. (To be published. Personal communication.)

MCCULLOCH, W. S. (1944) Chapter VII, in Bucy, P. C.: The Precentral Motor Cortex, Urb., Ill.

PENFIELD, W., SANTHA, K. VON, and CIPRIANI, A. (1939) *J. Neurophysiol.*, **2**, 257.

——, and HUMPHREY, S. (1940) *Arch. Neurol. a. Psychiat.*, **43**, 240.

——, and ERICKSON, T. C. (1941) Epilepsy and Cerebral Localization. Ch. C. Thomas, Springf., Ill.

SMITH, W. K. (1945) *J. Neurophysiol.*, **8**, 241.
TOWER, S. S. (1936) *Brain*, **59**, 408.
——, and HINES, M. (1944) Quot. From Hines, M., Chapter XVIII in Bucy, P. C.: The Precentral Motor Cortex, Urb., Ill.
WARD, A. A. (1948) *J. Neurophysiol.*, **11**, 13.
—— MCCULLOCH, W. S., and KOPELOFF, N. (1948) *J. Neurophysiol.*, **9**, 377.
WARD, J. W. (1948) Quot. Clark, G., and Ward, J. W., *Brain*, **71**, 332.
WHITTY, C. W. M. (1947) *Brain*, **70**, 416.
WILSON, S. A. KINNIER (1940) Neorology, Vol. II. Edward Arnold. Lond.

FURTHER STUDIES ON THE ROLE OF PROPRIOCEPTION IN CORTICALLY INDUCED MOVEMENTS OF THE FORELEG IN THE MONKEY[1]

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PREVIOUS studies from this laboratory showed the importance of proprioceptive impulses for the qualitative and quantitative response of the motor cortex to electrical stimulation [1, 2, 3]. It was demonstrated in particular that in the foreleg, stimulation of a biceps focus causes flexion of the elbow and extension of the wrist while stimulation of a more medially located triceps site induces an extension of the elbow and a flexion of the wrist. The quantitative response from the former site was increased by extension of the elbow and/or volar flexion of the wrist while flexion of the elbow and/or dorsal flexion of the wrist greatly facilitated responses from the triceps focus. The muscles of the "biceps-complex" were found to comprise in addition to the biceps the extensor carpi muscles while those of the triceps-complex consisted of the triceps and the flexor carpi muscles. These same complexes were also activated at the spinal level by stimulation of appropriate sensory nerves [4].

The purpose of this paper is to extend these observations on the organization of movement of the foreleg at the cortical level in two directions: first, by determining to what extent other muscles of the arm are functionally related to the biceps and triceps respectively; secondly, by investigating the influence of pronation and supination of the arm as well as of protraction and retraction of the shoulder on the responsiveness of an arm site in area 4 of the cortex.

METHOD

All experiments were performed on *Macacus rhesus* in dial-urethane anæsthesia. The motor cortex was stimulated at near-threshold voltage for 5 seconds with condenser discharges at varying frequencies, usually 80–90/sec., pulse duration 7.7 milliseconds. A period of three minutes was allowed to elapse between successive stimuli.

Electromyographic tracings were obtained by means of fine wire elec-

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trodes sewn into individual muscles. After suitable amplification, muscle potentials were recorded with a six channel ink-writing crystograph (Offner). Eleven muscles were usually studied in one experiment. They were recorded in groups of six with one muscle in common as a basis for comparison of results of successive stimuli on the same cortical point.

The animals were in lateral position during the experiments. The head was held in the Horsley-Clarke apparatus and the stimulating electrode adjusted by this instrument. All stimuli were applied 1–2 mm. anteriorly to the central fissure. The foreleg was fixated by a pin in the lower one-third of the humerus and a rubber shod clamp applied above the wrist.

With the animal in lateral position, retraction of the shoulder consisted of bringing the humerus posteriorly to a position in which it was parallel to the spinal column. In protraction the arm was brought forward until the humerus formed an angle of 90 degrees with the spinal column.

In experiments in which the position of the shoulder was not varied the arm was consistently held in a position of 45 degrees retraction. The wrist was allowed to flex naturally, about 25 degrees. Pronation and supination involved rotation of the forearm at the fixation point above the wrist through an arc of 90 degrees laterally and medially respectively.

Each of the figures shown here is based on numerous repetitions of a given postural change on stimulation of the same cortical point in the same animal. Every reaction was demonstrated in several animals. Only reversible reactions were evaluated. In some figures the return to the original response was omitted for brevity of illustration.

Results

I. The effect of fixation of the elbow at acute and obtuse angles (45 degrees and 150 degrees) on the reactivity of arm and shoulder muscles in response to cortical stimulation of biceps and triceps points.

Fig. 1 shows the effect of fixation of the elbow in extension and flexion on the reactivity of five arm and forearm muscles as a focus in the biphasic area [5] of the cortex (i.e. one which gives rise to movements involving both biceps and triceps complexes) was stimulated with 3·5 V. Activity in the brachioradialis and extensor digitorum communis corresponded to that of the biceps since it was increased when the elbow was fixated in extension. The palmaris longus and flexor digitorum sublimis manifested reciprocal activity and, together with the triceps, were facilitated by fixation of the elbow in flexion.

It was noted earlier [2, 5] that activity in one complex was usually associated with inhibition of the other, although with stimuli of greater

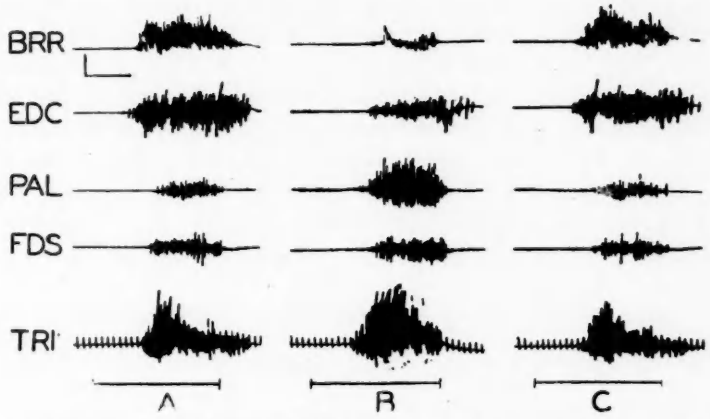

FIG. 1.—The effect of fixation of the elbow in flexion and extension on activity induced in arm and forearm muscles by stimulation of a biphasic cortical site. Stimulus 3·5 V, 66/sec. A-extension, B-flexion, C-extension. Extension of the elbow increased the response in the brachioradialis (BRR) and extensor digitorum communis (EDC), whereas flexion increased the response in the triceps (TRI), palmaris longus (PAL) and flexor digitorum sublimis (FDS).

intensity co-contraction might occur. This reciprocal activity is clearly shown in this figure and is further illustrated in fig. 2. The cortical site stimulated was 2 mm. lateral to the locus stimulated in the experiment of fig. 1. When the elbow was flexed there was a marked inhibitory

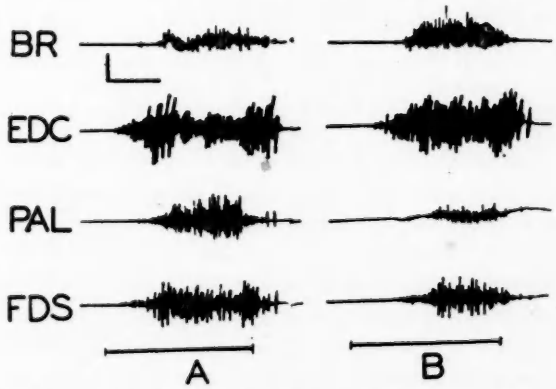

FIG. 2.—The effect of fixation of the elbow in flexion and extension, on activity induced in arm and forearm muscles by stimulation of a bi-phasic cortical site. Stimulus 3·5 V, 66/sec. A-flexion, B-extension. Note the inhibition of the extensor digitorum communis (EDC), when the elbow was flexed, which coincided with the period of activity in the palmaris longus (PAL). In extension the components of the biceps-complex (brachialis, extensor digitorum) are maximal, those of the triceps-complex (palmaris, flexor digitorum) minimal.

effect on the EMG response of the extensor digitorum communis to cortical stimulation. The duration of the inhibition in this muscle corresponded with the period of greatest activity in the palmaris longus (triceps-complex) and the triceps itself (not shown). Fixation of the elbow in extension was associated with an increased amplitude of the EMG response in the extensor digitorum communis as well as in biceps (not shown) and brachialis, while the responses in the palmaris longus and flexor digitorum sublimis were diminished.

Fig. 3 shows the effect of proprioception on the EMG responses to

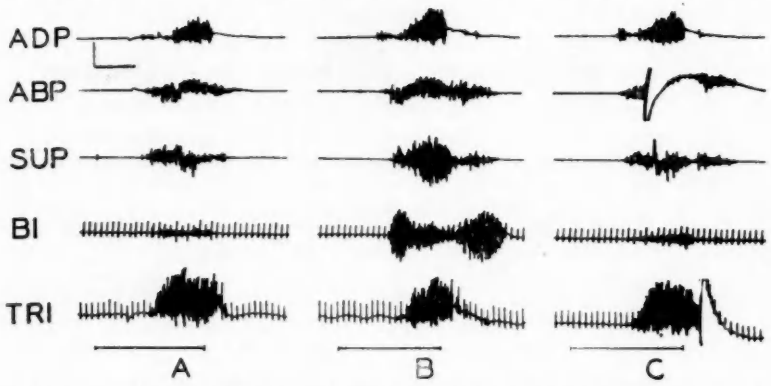

FIG. 3.—The effect of fixation of the elbow in flexion and extension, on activity induced in arm and forearm muscles by stimulation of a biphasic cortical site. Stimulus 1·5 V, 53/sec. A-flexion, B-extension, C-flexion. Responses in the biceps (BI), supinator (SUP), abductor pollicis (ABP) and adductor pollicis (ADP), were greater when the elbow was extended. Triceps (TRI) activity was greatest when the elbow was flexed. Note the inhibition of the biceps in B, coinciding with activity in the triceps. After-discharge did not appear in the biceps until triceps activity ceased.

cortical stimulation in other forearm muscles. Stimulation of a biphasic cortical site induced responses of relatively low amplitude in the biceps, supinator, abductor pollicis and adductor pollicis when the elbow was fixated in flexion. When the elbow was extended there was a distinctly increased response in the supinator, abductor pollicis and adductor pollicis. The EMG of the biceps was also increased and that of the triceps distinctly diminished. Whereas the biceps response with the elbow flexed consisted of a minor co-contraction simultaneous in onset with activity in the triceps, it was found that when the elbow was extended activity in the biceps was increased in duration and magnitude and showed a clear-cut inhibition corresponding with the period of activity in the triceps. On cessation of the stimulus there followed a rebound after discharge in the biceps, which did not begin, however, until triceps activity also had

ceased. Since the activity in the supinator, abductor pollicis and adductor pollicis paralleled that of the biceps when the elbow was fixated in extension, they are considered to be components of the biceps complex. It is interesting to note that these forearm and finger muscles although paralleling in general the responsiveness of the biceps are not inhibited during the period of triceps activity as is the biceps.

The proprioceptive effects induced by fixation of the elbow in flexion or extension are not limited to muscles moving the elbow and hand. Fig. 4 shows that the EMG response in the acromio-deltoid, on stimulation of a biceps cortical site, corresponded with that in the brachialis and brachioradialis, in that each was increased when the elbow was extended. Activity in the pronator teres was also considerably greater when the elbow was extended than when it was flexed.

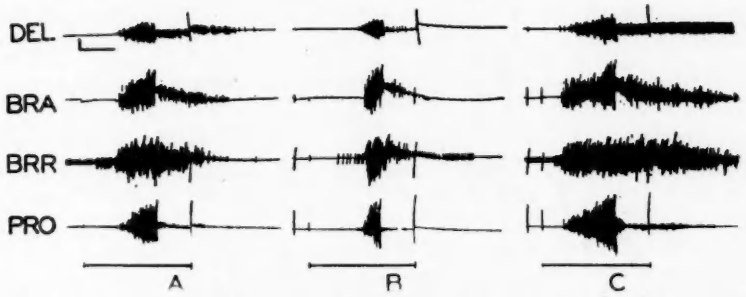

FIG. 4.—The effect of fixation of the elbow in flexion and extension on activity induced in arm, forearm and shoulder muscles by stimulation of a biceps cortical site. Stimulus 2·6 V, 30·3/sec. A-extension, B-flexion, C-extension. Extension of facilitated responses in the acromio-deltoid (DEL), brachialis (BRA), brachioradialis (BRR) and pronator teres (PRO). Note change of summation time.

In general it was found that of the shoulder muscles only the acromio-deltoid could be activated regularly from cortical biceps sites whereas other muscles of the shoulder contracted on stimulation of the triceps sites. Here again the parallelism between the amplitude of the EMG of triceps and shoulder muscles was used as basis for the classification of these muscles in the triceps-complex. It was found that trapezius, pectoralis major and infraspinatus showed an increased response to cortical stimulation of a triceps site when the elbow was fixated at an acute angle as compared to the reaction observed in these muscles at an obtuse angle of the elbow.

The relation between cortical sites and reaction of shoulder muscles is illustrated in fig. 5. In the upper section of fig. 5, activity was recorded in the trapezius, pectoralis major[1], latissimus dorsi[1], acromio-deltoid and

[1] Not shown in the figure.

triceps. The association of the trapezius with the triceps on flexion of the elbow and its inverse relation to the biceps was clearly shown. The acromio-deltoid activity paralleled that of the biceps, being greatest when the elbow was extended, as noted previously. In the flexor position, marked inhibition of the acromio-deltoid coincided with slightly increased activity in components of the opposite complex (trapezius, triceps).

The lower section of fig. 5 shows that when the cortical site was moved

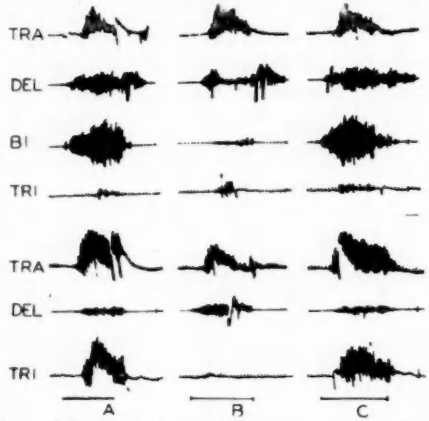

FIG. 5.—The effect of fixation of the elbow in flexion and extension on activity induced in arm and shoulder muscles. Points stimulated were separated by 2 mm. Upper section: A biphasic point was stimulated with 3·0 V, 83/sec. The acromio-deltoid (DEL) was inhibited in flexion, during trapezius (TRA) and triceps (TRI) activity. A-extension, B-flexion, C-extension. Lower section: A triceps point was stimulated with 3·5 V, 83/sec. Note change of sequence in this section, A-flexion, B-extension, C-flexion.

2 mm. medially (same experiment) along the central fissure, the triceps zone had clearly been entered. The amplitudes of the biceps[1] and acromio-deltoid reactions were then small, even when the elbow was extended. The fundamentally different reaction of the acromio-deltoid as compared to the trapezius muscle is clearly seen since the former shows its optimal reaction with the elbow extended, the latter with the elbow flexed. In addition it is seen, as the site of cortical stimulation was moved more medially, that the reactivity of the trapezius increased and that of the acromio-deltoid diminished. It may also be noted that proprioceptive modification of the activity of the shoulder muscles was greatest for the acromio-deltoid in a more lateral (biceps) site and for the trapezius in a more medial (triceps) site. These experiments indicate that the shoulder muscles (acromio-deltoid excepted) are associated with the triceps in two ways. Activity is induced in these muscles most easily

[1] Not shown in the figure.

by stimulation of a medial foreleg cortical site (triceps site), and such activity is facilitated proprioceptively by fixation of the elbow in flexion.

Fig. 6 shows the response of a different shoulder muscle, the pectoralis major, to cortical stimulation. A triceps site was stimulated when the elbow was fixated in flexion and extension. Activity induced in the pectoralis major paralleled that of the trapezius and triceps. Flexion of the elbow facilitated the response in those three muscles.

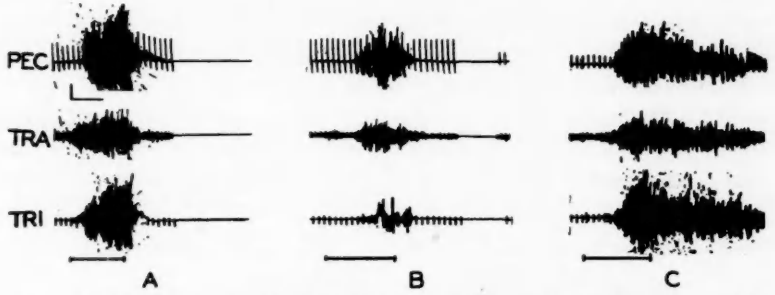

FIG. 6.—The effect of fixation of the elbow in flexion and extension on activity induced in shoulder muscles by stimulation of a triceps site. A-flexion, B-extension, C-flexion. Stimulus 3·5 V, 90/sec. The triceps (TRI), trapezius (TRA) and pectoralis major (PEC) responses were facilitated by flexion of the elbow.

On the basis of this type of experiment the concept of the biceps and triceps complex has to be extended considerably. It comprises arm and shoulder muscles as well, as Table I indicates. During the course of these experiments it was noted that occasionally reactions in some of the shoulder muscles listed in Table I under triceps-complex appeared also but to a lesser degree on stimulation of a biceps point. In general, their reactivity was small and not markedly modified by changes in the

TABLE I.—MUSCLES CONSTITUTING BICEPS AND TRICEPS COMPLEXES

Biceps-complex	*Triceps-complex*
Biceps	Triceps
Extensor carpi radialis	Flexor carpi ulnaris
Extensor carpi ulnaris	Flexor carpi radialis
Extensor digitorum communis	Palmaris longus
Pronator teres	Flexor digitorum sublimis
Abductor pollicis longus	Flexor digitorum profundus
Adductor pollicis	Dorso-epitrochlearis
Supinator	Pectoralis major
Extensor digitorum proprius II and III	Trapezius
Extensor digitorum proprius III and IV	Latissimus dorsi
Brachioradialis	Infraspinatus
Brachialis	Supraspinatus
Acromio-deltoid	Spino-deltoid
	Teres major

elbow position although these same muscles showed characteristic variations in responsiveness when stimulated from a triceps site. In some instances, however, it was noted that the grouping into the biceps or triceps complex could not be made since a muscle showed significant changes in responsiveness to variations in the elbow position from both triceps and biceps sites. Such an example is given in fig. 7. When the

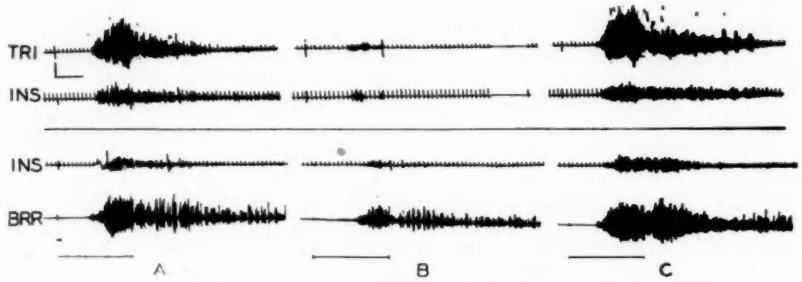

FIG. 7.—The effect of fixation of the elbow in flexion and extension on activity induced in arm and shoulder muscles by stimulation of biceps and triceps cortical sites. Upper section: Stimulus 4·5 V, 47/sec. Stimulation of a triceps site. A-flexion, B-extension, C-flexion. Triceps (TRI) and infraspinatus (INS) responses were greater when the elbow was flexed. Lower section: Stimulus 5·7 V, 90/sec. Stimulation of a biceps site. A-extension, B-flexion, C-extension. The infraspinatus response was greater at this site when the elbow was extended. Its response paralleled that of the brachioradialis.

elbow was flexed, cortical stimulation of a triceps site induced strong activity in the triceps and infraspinatus, with prolonged after-discharge in both muscles. Fixation of the elbow in extension was associated with very low amplitude activity in both muscles and complete absence of after-discharge. The lower part of fig. 7 shows the reactivity of a muscle of the biceps-complex (brachioradialis) with that of the infraspinatus at different positions of the elbow as a biceps site was stimulated. The optimal reaction appeared in both muscles with fixation of the elbow in extension.

II. The effect of fixation of the shoulder in protraction and retraction on the reactivity of arm, forearm and shoulder muscles in response to cortical stimulation of biceps and triceps sites.

A series of experiments was performed in which various points in the forearm area were stimulated while the shoulders was fixated in different degrees of protraction or retraction. It was found that with the fixation of the shoulder in protraction the responsiveness of arm and shoulder muscles was greatly increased. This effect was seen on stimulation of biceps as well as of triceps sites. The chief effect of protraction of the shoulder was seen when the angle of the humerus in the experiment

was 90 degrees; further protraction did not appreciably increase the response.

The rules previously stated, that with the elbow in flexion the responsiveness of the triceps-complex increases while that of the biceps-complex decreases, and the converse of this statement, remain valid under conditions involving protraction of the arm, i.e. cortical stimulation induces greater activity in the triceps-complex when the arm is protracted with the elbow flexed than when the arm is protracted with the elbow extended. Likewise, optimal facilitation of the biceps-complex is obtained by protraction of the arm when the elbow is extended.

Fig. 8 shows that on stimulation of a triceps site with the elbow

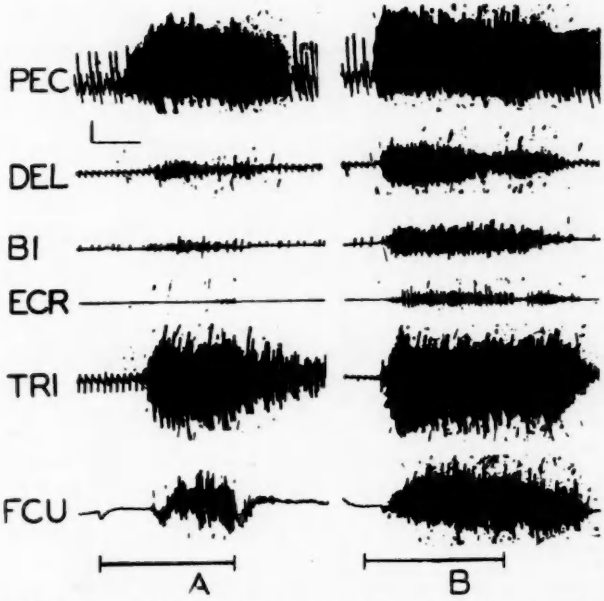

FIG. 8.—The effect of fixation of the shoulder in protraction and retraction on activity induced in arm, forearm and shoulder muscles by stimulation of a triceps cortical site. Elbow flexed, stimulus 3·8 V, 80·3/sec. A-retraction, B-protraction. Protraction increased the response in the pectoralis major (PEC), triceps (TRI) and flexor carpi ulnaris (FCU). Contraction in biceps (BI), acromio-deltoid (DEL) and extensor carpi radialis (ECR) was also facilitated.

fixated in flexion the response in the triceps-complex increases with protraction of the shoulder. At the same time the minimal reaction appearing in the biceps-complex (biceps, extensor carpi, and acromio-deltoid) during retraction of the shoulder is likewise distinctly increased when the shoulder is fixated in protraction. Similar reactions were found on

stimulation of a biceps point, i.e. the responsiveness of the biceps-complex increased with protraction of the shoulder and the lesser reactions of muscles belonging to the triceps-complex were also augmented. In experiments with threshold stimuli it was noted that the summation time of shoulder and arm muscles was greatly decreased with the elbow fixated in protraction. In the experiment illustrated in fig. 9 in which a biceps site was stimulated with the elbow fixated in extension, the responsive-

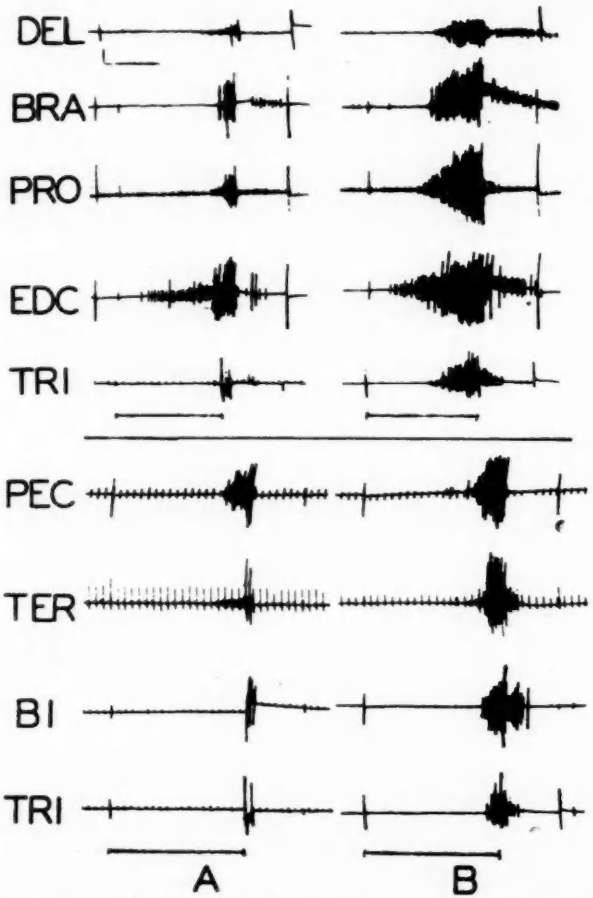

FIG. 9.—The effect of fixation of the arm in protraction and retraction on activity induced in arm, forearm and shoulder muscles by stimulation of a biceps cortical site. Elbow extended, stimulus 2·6 V, 30·5/sec. A-retraction, B-protraction. Responses of the acromio-deltoid (DEL), brachialis (BRA), pronator teres (PRO), extensor digitorum communis (EDC), triceps (TRI), pectoralis major (PEC), teres major (TER) and biceps (BI) were increased by protraction. Note the change in summation time.

ness of muscles in the biceps-complex and that of the triceps and those shoulder muscles which commonly respond to stimulation of triceps sites (pectoralis, teres major) were increased on protraction of the shoulder. Although the experiments of fig. 8, in particular the increased reactivity of biceps and extensor carpi in protraction, could well be explained as increased co-contraction accompanying the greatly augmented response of the triceps-complex, such an interpretation is hardly applicable to the experiment illustrated in fig. 9, in which threshold reactions are recorded. It therefore seems justified to conclude that protraction of the shoulder increases unspecifically the responsiveness of arm muscles to cortical stimulation, thereby tending to produce an innervation pattern of fixation rather than that of reciprocal innervation.

III. The effect of fixation of the forearm in pronation and supination on the reactivity of arm, forearm and shoulder muscles to cortical stimulation of triceps and biceps points.

The effects of pronation and supination of the forearm on motor responses to cortical stimulation are distinct and specific. On a biceps cortical point the biceps-complex is facilitated by pronation whereas on a triceps cortical point the triceps-complex is facilitated by pronation. In each case the activity of the antagonistic group is increased by supination. In these experiments the cortical site stimulated is the determining factor as to which muscle complex is facilitated by a given postural change.

These responses were best seen if the elbow was extended when a biceps point was stimulated, and flexed when a triceps point was stimulated. In the reversed elbow positions the stimulation of respective cortical points introduced variations which were at times difficult to interpret.

Stimulation of a cortical triceps site shows in fig. 10 that the EMG

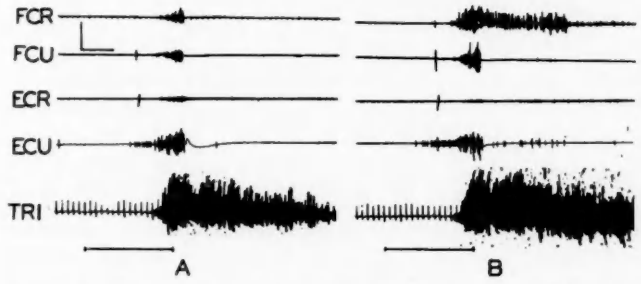

FIG. 10.—The effect of fixation of the forearm in pronation and supination on activity induced in arm and forearm muscles by stimulation of a cortical triceps site. Elbow flexed, stimulus 3·5 V, 83/sec. A-supination, B-pronation. Responses in the triceps (TRI), flexor carpi ulnaris (FCU), and flexor carpi radialis (FCR) were increased on pronation. The extensor carpi ulnaris (ECU) and extensor carpi radialis (ECR) were greater on supination of the forearm.

activity in the triceps is greater in pronation, as indicated by the increased amplitude and length of the after-discharge. Similar changes occur in the forearm components of the triceps-complex (the flexor carpi radialis and ulnaris). The flexor carpi radialis shows an after-discharge which is not present when the forearm is supinated. The muscles of the biceps-complex, the extensor carpi radialis and extensor carpi ulnaris, show the greatest response to cortical stimulation when the forearm is supinated though the change is slight.

The importance of the cortical site stimulated, in determining which muscle complex is facilitated by pronation of the forearm, is shown in fig. 11. The upper section shows the EMG activity in the triceps and a group of biceps-complex muscles when a triceps cortical site is stimulated (with the elbow flexed). The triceps is facilitated by fixation of the forearm in pronation, whereas supination of the forearm is the favourable position for activity in response to cortical stimulation in the extensor digitorum proprius II and III, abductor pollicis longus and extensor digitorum proprius III and IV, i.e. muscles which form part of the biceps-complex. In the biceps there is a small co-contraction that increased in pronation along with the increased activity in the triceps.

The lower section of fig. 11 shows the change in the responses when the stimulating electrodes are shifted to a biceps cortical site. Activity of the triceps in response to cortical stimulation is now confined to a small co-contraction paralleling biceps activity while the biceps response is facilitated by fixation of the forearm in pronation. The responses of the extensor digitorum proprius III and IV and abductor pollicis are facilitated by pronation, whereas previously supination had been the more favourable position. In this section the EMG response in the extensor digitorum proprius II and III is essentially unchanged.

Another example of the action of pronation and supination on the reactivity of a biceps site in the motor cortex is illustrated in fig. 12. Its stimulation results in a typical biceps-extensor carpi response while activity in the flexor carpi which belongs to the triceps-complex was minimal. The quantitative relation between these two reactions was altered significantly by pronation and supination. In the former condition biceps and extensor carpi showed a larger reaction and a shorter summation time in pronation than in supination while the flexor carpi showed an augmented response in supination which appeared during stimulation and particularly in the after-discharge.

Fig. 13 illustrates that pronation and supination have also an effect on the shoulder muscles. In this experiment stimulation of a biceps point elicited a contraction in biceps and acromio-deltoid muscles with a co-contraction in the triceps. The experiment reproduced in the sections

B to D was performed while the elbow was flexed whereas this joint was fixated in extension in A and E. The figure shows that even in the unfavourable elbow position (elbow fixated at an acute angle) pronation increases the responsiveness of the flexor complex on stimulation of a

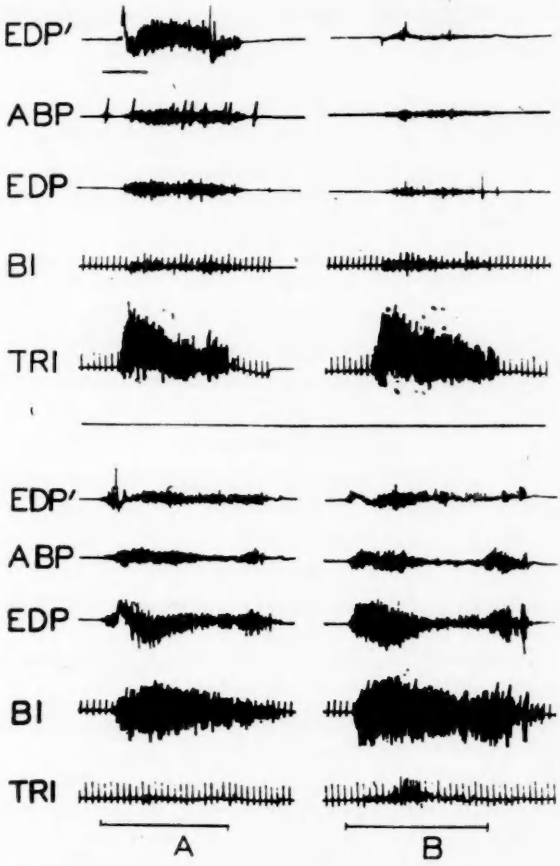

FIG. 11.—The effect of fixation of the forearm in pronation and supination on activity induced in muscles of the arm and forearm by stimulation of a triceps and a biceps cortical site. A-supination, B-pronation. Upper section: Stimulation of a triceps site. Elbow flexed, stimulus 1·9 V, 90/sec. Triceps (TRI) and biceps (BI) responses (the latter a co-contraction) were greater when the forearm was pronated. The extensor digitorum propius II and III (EDP), abductor pollicis (ABP) and extensor digitorum proprius III and IV (EDP) responses were greater on supination. Lower section: Stimulation of a biceps site. Elbow extended, stimulus 3·0 V, 50/sec. The biceps-complex (biceps, extensor digitorum proprius III and IV and abductor pollicis) was facilitated in pronation. The extensor digitorum proprius II and III was essentially unchanged.

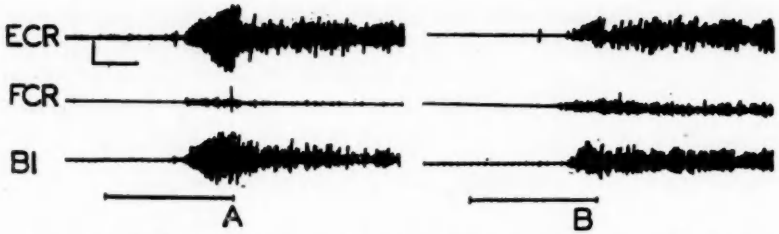

FIG. 12.—The effect of fixation of the forearm in pronation and supination, on activity induced in arm and forearm muscles by stimulation of a biceps cortical site. Elbow extended, stimulus 3·0 V, 42/sec. A-pronation, B-supination. Pronation facilitated the responses in the biceps (BI) and extensor carpi radialis (ECR). The flexor carpi radialis (FCR) was facilitated by supination. Note the after-discharge in this muscle, not present in pronation.

biceps site. It shows also that the effect of changes in the position of the elbow is far greater than that produced by pronation or supination.

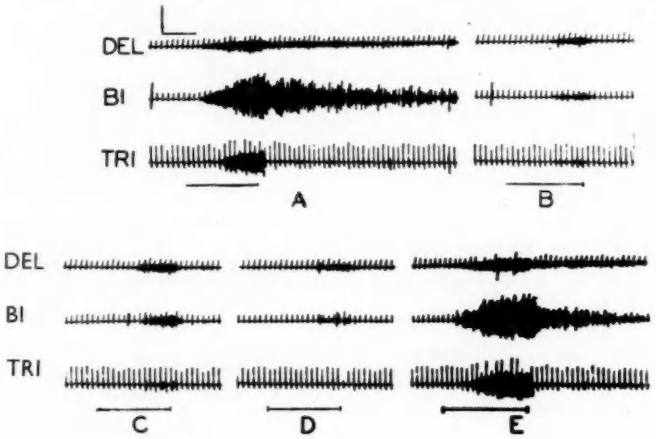

FIG. 13.—The effect of fixation of the forearm in pronation and supination on activity in arm and shoulder muscles induced by stimulation of a biceps cortical site. Stimulus 4·5 V, 102/sec. Trapezius (TRA), acromio-deltoid (DEL), biceps (BI) and triceps (TRI). A and E—elbow extended, B to D—elbow flexed, B—forearm supinated, C—forearm pronated, D—forearm supinated. In A and E the arm is in a position intermediate between pronation and supination.

COMMENT

Previous investigations [1, 2] which demonstrated for a limited number of muscles and position the importance of proprioceptive impulses for the quantitation of the cortically induced muscular responses have been greatly expanded in the present study. The earlier work showed that on stimulation of the foreleg area in the motor cortex the muscles are activated in

certain functional groups which were classified as biceps and triceps complexes respectively. The present experiments show that the biceps-complex comprises not only the biceps and extensor carpi muscles but also the extensors of the fingers and the abductor and adductor pollicis. Stimulation of a biceps focus activates at the same time the brachialis and brachioradialis muscles. Apparently, the movement which results from stimulation of biceps site is characterized by flexion of forearm and extension of wrist and fingers (Bosma and Gellhorn [5]). Moreover, and this is the chief criterion upon which this classification is based, fixation of the elbow in extension increases not only the amplitude of the EMG in the biceps but also in the other muscles constituting the biceps-complex. It was also found in agreement with our earlier studies that fixation of the wrist in volar flexion increases not only the reactivity of the extensor carpi but also that of other components of the biceps-complex which act on elbow, wrist, or phalangeal joints. It is interesting to note that the supinator is likewise included in this complex since biceps action and supination are intimately inter-related. The appearance of the pronator muscle in the biceps group is not unexpected since it acts as a flexor of the forearm "when the bones of this segment are fixed to prevent pronation" (Hartman and Straus [8]).

On the basis of similar criteria the triceps-complex appears to consist not only of triceps and carpal flexors but also of the dorso-epitrochlearis and the flexors of the palm and fingers. The responses in these muscles are intensified when either the elbow is fixated at an acute angle or the wrist is held in dorsiflexion.

Obviously, gradation of the whole or of parts of each of the two muscle groupings can be achieved not only by variations in frequency and intensity of cortical stimulation which remains effective in the deafferented extremity (Hyde and Gellhorn [3]) but also by postural changes affecting one or more joints of the limb. Since the summation time is also modified by proprioceptive impulses (cf. figs. 2, 5, 8, 9 and 14 and Gellhorn [2]) it may be said that spatial and temporal co-ordination of a muscle group is modified by proprioceptive impulses particularly under conditions involving nearly isometric contraction, i.e. fixation [1, 2]. It is interesting to note that with stimulation of near-threshold intensity the concept of reciprocal innervation remains valid for these complex muscle groups.

The shoulder muscles may likewise be related to the biceps and triceps complexes but this division is not as sharp as that of the arm muscles. In general the acromio-deltoid muscle was found to be associated with the biceps-complex, and other shoulder muscles (particularly trapezius, spino-deltoid, supraspinatus, pectoralis major, and teres major) with the

triceps-complex. This statement is again based on the fact that these muscles contract on stimulation of a biceps or triceps site in the motor cortex and that their responsiveness as judged by the amplitude and summation time of the EMG is modified with that of the biceps and triceps when the fixation of elbow and wrist are altered. However, it must be admitted that the cortical areas for biceps and triceps do not exactly coincide with those of the shoulder muscles (cf. fig. 6) and that occasionally this division of the shoulder muscles does not hold since some muscles show activity on stimulation of a cortical biceps as well as a triceps focus.

The close association of shoulder to arm muscles on cortical stimulation is furthermore illustrated by the study of the effect which changes in the posture of the shoulder exert on the responsiveness of the arm muscles. It was found that stimulation of a biceps or triceps site caused a minimal action with the arm retracted, other conditions being equal. The reactivity increased with increasing protraction and was approximately maximal when the angle between the longitudinal axis of the body and the humerus was 90 degrees. Further protraction did not materially alter this effect. This action of protraction of the arm was shown to be non-specific. In response to cortical stimulation, protraction facilitated the activity in muscles of the triceps and biceps complexes, when either a triceps or a biceps cortical site was stimulated.

This result is interesting inasmuch as it seems to indicate that protraction leads to contractions in agonists and antagonists, i.e. it favours fixation. However, even under these conditions reciprocal innervation is not absent. Although, e.g. stimulation of a triceps site in protraction of the arm leads to increased reactivity in all responding muscles which may belong to the biceps as well as the triceps complex, changes in the position of the elbow will still have their typical effects; that is, the EMGs of the biceps-complex show an increased amplitude with the fixation of the elbow at an obtuse angle while the behaviour of the triceps-complex is the reverse.

A novel principle in the organization of cortically induced movements is introduced by the experiments on pronation and supination which illustrate that the cortical site of stimulation is an important factor in determining the nature of modification of cortically induced activity by a given posture. It was found that, with constant fixation of the arm pronation facilitated responses of biceps-complex muscles to cortical stimulation when a biceps site was stimulated, whereas the movements of the triceps-complex were facilitated by the same postural condition when a triceps cortical site was stimulated. In each case, antagonistic muscles (those of the opposite complex) were facilitated by the opposite postural change, i.e. supination. The proprioceptive modification of cortically induced activity

by pronation and supination of the forearm, extends to shoulder muscles such as the trapezius and teres major which undergo parallel changes.

Proprioceptive facilitation resulting from fixation of the elbow at an acute or an obtuse angle was previously shown to determine the relative reactivity of foreleg muscles from any cortical site in the foreleg area; or, to express this matter somewhat differently, the proprioceptive condition (posture of the arm) for an optimal response of the biceps-complex is pessimal for the triceps response and this statement holds for various biceps and triceps cortical sites. The effect of pronation and supination, however, is determined by both the cortical site and the peripheral posture which modifies the reactivity of the centre through proprioceptive impulses. This difference in the action of flexion and extension of the elbow as compared to pronation and supination may be related to the greater effectiveness of the former (cf. fig. 13).

The proprioceptive tuning of the nervous system has three aspects: in the first, represented by the action of fixation of the elbow (flexion or extension), the modification of the cortically induced activity is predictable without the knowledge of the cortical site stimulated; in the second, represented by action of pronation and supination, predictability of the results depends on the knowledge of the site of cortical stimulation as well. Apparently a third form of interaction between proprioceptive factors and cortical stimulation was seen with certain shoulder muscles such as the infraspinatus which reacted optimally from a biceps site with fixation of the elbow at an obtuse angle and similarly from a triceps site with the elbow fixated at an acute angle. This seems to indicate that certain shoulder muscles are somewhat loosely connected with the biceps and triceps complexes and that with increasing intensity of the response in the agonist an increase in the activity of an associated shoulder muscle such as the infraspinatus may be seen.

The various types of proprioceptive modification of the effects of stimulation of the motor cortex are summarized in Table II (p. 520).

The neglect of the complex but well defined and powerful influence which proprioceptive tuning exerts on the responsiveness of cortical foci may be one of the factors which accounts for the marked individual variability shown in the maps of the motor cortex in higher animals and man [6, 7].

Summary

The reactivity of most of the arm and shoulder muscles on stimulation of the motor cortex was studied in the monkey (*Macacus rhesus*) in different conditions of fixation of shoulder, elbow and wrist joints in order to elucidate further the role of proprioceptive impulses in cortically induced movements.

TABLE II.—TYPES OF PROPRIOCEPTIVE ACTION ON THE RESPONSIVENESS OF THE MOTOR CORTEX

I	Fixation of elbow	Acute angle	Triceps-complex increased	Biceps-complex inhibited
		Obtuse angle	Biceps-complex increased	Triceps-complex inhibited

This result is independent of the site of cortical stimulation. Experiments illustrate validity of the principle of reciprocal innervation for biceps- and triceps-complexes

		Triceps site	*Biceps site*
II	Pronation	Increases triceps-complex	Increases biceps-complex
		Decreases biceps-complex	Decreases triceps-complex
	Supination	Decreases triceps-complex	Decreases biceps-complex
		Increases biceps-complex	Increases triceps-complex

Results are determined by proprioceptive impulses *and* the cortical site

III	Fixation of elbow	Acute angle	Increases supraspinatus from triceps site
		Obtuse angle	Increases supraspinatus from biceps site

Optimal proprioceptive conditions for cortical site may increase responsiveness of some shoulder muscles

IV	Protraction of shoulder	Increases biceps- and triceps-complexes
	Retraction of shoulder	Decreases biceps- and triceps-complexes

Effect is independent of cortical site. Protraction tends to call forth contraction in agonists and antagonists (tendency to fixation)

The biceps-complex was found to consist largely of the flexors of the elbow, the extensors of wrist and fingers and the acromio-deltoid muscle while the triceps-complex comprised, in addition to the extensors of the elbow, the flexors of the wrist and fingers and most of the shoulder muscles with the exception of the acromio-deltoid muscle. This classification was based on the fact that fixation of the elbow in extension increased the responsiveness to cortical stimulation of a specific functional group (biceps-complex) while fixation of the elbow at an acute angle increased the response in a functionally antagonistic group (triceps-complex). Proprioceptive facilitation appeared also as a result of fixation of the wrist. In dorsiflexion of the wrist it increased the responsiveness of the triceps-complex, in volar flexion that of the biceps-complex. Activity in one functional unit was usually associated with inhibition of the other. With intense reactions co-contraction may occur.

Fixation of the shoulder in protraction facilitated the response to cortical stimulation non-specifically, i.e. activity in muscles of both complexes was facilitated. This suggests a tendency toward fixation of elbow and wrist under these conditions. However, even then the principle of reciprocal innervation is not abolished since with the arm protracted the cortically induced response is changed by the position of the elbow according to the above stated rules.

Pronation of the forearm facilitated the activity in the biceps or triceps complex, depending upon the cortical site stimulated. The rule is summarized in the following table.

	Triceps site	*Biceps site*
Pronation	Triceps-complex increased	Biceps-complex increased
	Biceps-complex decreased	Triceps-complex decreased
Supination	Triceps-complex decreased	Biceps-complex decreased
	Biceps-complex increased	Triceps-complex increased

The functional grouping of shoulder muscles is in some instances dependent on the cortical site inasmuch as it was found that the response of the infraspinatus was optimal from a biceps site with the elbow fixated at an obtuse angle while a maximal reaction occurred from the triceps site when the elbow was fixated at an acute angle.

The proprioceptive reinforcement of cortically induced movements may be classified into three groups:

(1) Muscle stretch and particularly tension produced during isometric contraction resulting from activity of muscles under conditions of fixation, selectivity increases the responsiveness in this muscle and in functionally related muscles while that of the antagonists is diminished. This rule is best illustrated by the effect of fixation of the elbow at an acute or obtuse angle on the triceps or biceps complex in cortically induced movements.

(2) Protraction of the shoulder increases the responsiveness in arm and shoulder muscles activated by stimulation of any point of the foreleg area of the motor cortex. This effect tends to create conditions of fixation since protraction increases activity in agonists as well as in antagonists.

(3) Pronation facilitates the responsiveness of the agonists (i.e. of the triceps-complex from a triceps site and of the biceps-complex from a biceps site). Optimal facilitation of the antagonists is seen in supination. The effects of pronation and supination on the responsiveness of the motor cortex cannot be stated with respect to a muscle or a muscle group —this is in contrast to rule 1—but must take into account the cortical site stimulated.

REFERENCES

[1] GELLHORN, E. (1948) *Brain,* **71**, 26.
[2] —— (1949) *Brain,* **72**, 35.
[3] HYDE, J., and GELLHORN, E. (1949) *Am. J. Physiol.,* **156**, 311.
[4] LOOFBOURROW, G. N., and GELLHORN, E. (1949) *J. Neurophysiol.,* **12**, 435.
[5] BOSMA, J. F., and GELLHORN, E. (1947) *Brain,* **70**, 127; (1946) *J. Neurophysiol.,* **9**, 263.
[6] MURPHY, J. P., and GELLHORN, E. (1945) *Arch. Neurol. and Psychiat.,* **54**, 256.
[7] PENFIELD, W. (1947) *Proc. Assoc. Nerv. and Ment. Dis.,* **26**, 1.
[8] HARTMAN, C. G., and STRAUS, W. L. (1933) The Anatomy of the Rhesus Monkey. Baltimore.

A STUDY OF RETROGRADE DEGENERATION IN THE OCULOMOTOR NUCLEUS OF THE RHESUS MONKEY, WITH A NOTE ON A METHOD OF RECORDING ITS DISTRIBUTION

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In 1892 Nissl, who had previously described the normal appearance of the chromatin granules of neurones, demonstrated the phenomena of retrograde degeneration in the facial nucleus after avulsion of its nerve. The same paper introduced the use of methylene blue as a stain for chromatin material. The method was at once applied to the study of the oculomotor nuclei by such workers as Schwabe (1896), Bernheimer (1897), and Bach (1899). Bernheimer, whose work has remained most significant, since it was carried out on a primate, the rhesus monkey, extirpated individual ocular muscles, and claimed to have produced thereby localized groups of oculomotor neurones which displayed the characteristics of retrograde degeneration. The pattern of representation of the extrinsic ocular muscles which Bernheimer described was largely confirmed by an extensive analysis of experimental, clinical, and pathological literature made by Brouwer (1918), and his findings still form the basis of the textbook description, despite discordant physiological results published in recent years.

About the same time, however, Warrington (1898), in a critical study of chromatolysis in several different animals, recorded the absence of clear retrograde degeneration in the oculomotor nucleus of a rhesus monkey, killed twenty-eight days after unilateral division of the oculomotor nerve. Apart from this paper, as Bucy (1928) has pointed out, the excellence of Nissl's work has discouraged criticism of his findings until recent years. Bucy (1928) paid special attention to the time factor in chromatolysis. Geist (1933) has discussed various factors, such as the age and species of animal, type of neurone, the distance of division from the cells of origin, and the time element. Bodian and Mellors (1945) studied the cycle of events in the motor neurones of the sciatic nerve of the rhesus monkey after peripheral division of the nerve. These findings will be discussed later; but, apart from Warrington's solitary case, there appears to have been no attempt to re-examine the question of retrograde degeneration in the rhesus oculomotor nuclei. In view of this animal's importance as the one of choice in research such as Bern-

heimer's into the topography of the oculomotor nuclei, the material of this study has been examined primarily to assess the reliability of such methods in this particular nucleus.

Materials and Methods

The material of this study consisted of the mid-brains of rhesus monkeys (*Macaca mulatta*). Under intravenous Kemithal anæsthesia, intracranial division of the right or left oculomotor nerve in the interpeduncular space was carried out, the operations being performed by Mr. R. A. Bailey. Full aseptic precautions were taken. The method of division was by diathermy or sharp hook. In each case, after ten or eleven days, the animal was killed by an overdose of Kemithal, ex-sanguinated, and perfused first with normal saline and then with 10 per cent. formol saline. The whole brain was removed a few hours later, and the mid-brain, isolated by transverse sections at the levels of the upper borders of the pons and the mid-brain was carried through alcohols in the usual manner to paraffin wax.

Satisfactory division of the nerve was in every case observed during removal of the brain, but as a precaution Marchi degeneration of the trunk of the nerve distal to section was demonstrated. In some cases also photographs of the animal's eyes were taken after recovery from operation. Ptosis, mydriasis, and extensive ophthalmoplegia were present in every case.

Serial sections, of 10 μ thickness and in a plane transverse to the aqueduct were cut through the entire mid-brain of six animals—one normal and five after operation. A further mid-brain was cut coronally, in the plane of the aqueduct. All sections were mounted, stained and later examined.

A number of staining techniques were used. The first series was stained by toluidine blue, and carbol thionin was also tried; but both these retrogressive methods, like the original Nissl technique, necessitate careful and individual differentiation and were found to be very tedious, since each series comprised 150–200 slides. For the same reason Borrel's methylene blue was also used only as an occasional check stain for comparison. Einarson (1932) introduced a technique for Nissl granules which employs gallocyanin and requires no differentiation. It has proved highly suitable for bulk staining. The pH of the stain was adjusted to 3·81 by means of N/100 sodium hydroxide, and the slides were immersed in it for forty-eight hours, as in the original Einarson technique. By increasing the concentration of the stain ten times and using it at 60–65° C. in an incubator, the staining time could be reduced to 30–50 minutes, but the results of this rapid method were not found

to be as satisfactory as those attained by the usual method. Eosin was sometimes used as a counterstain, but was frequently omitted, since it was found to be easier to examine sections which had not been counterstained.

In each series except the normal one every tenth section containing the oculomotor nuclei (and usually the rostral extremity of the trochlear nuclei) was photographed at a magnification of 100. Whole plate enlargements of these fields were made (fig. 10), and the photographs were used with the corresponding sections at microscopic examination. It was found quite easy to identify individual neurones in the photograph, and the condition of these was noted under high power and indicated on the photograph by an appropriate symbol or coloured dot in waterproof ink. The photographs were then bleached, thus leaving clear patterns of the distribution of normal and degenerating neurones at intervals of 100 μ throughout the length of the oculomotor nuclei (figs. 11–13). Each series comprised about 30 such charts, providing a permanent spatial record of the state of neurones in the nuclei. Counts were made of normal and chromatolytic cells, both ipsilateral and contralateral with regard to the nerve division, for comparison of the results obtained in the different series.

FIG. 11 (for caption *see opposite page*).

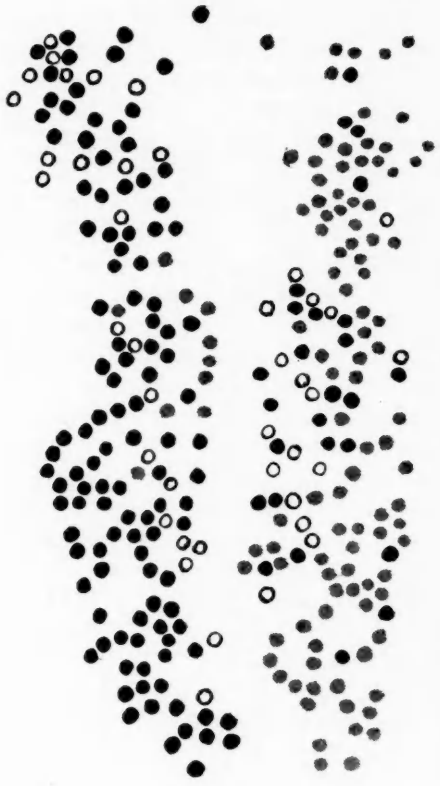

FIG. 12.

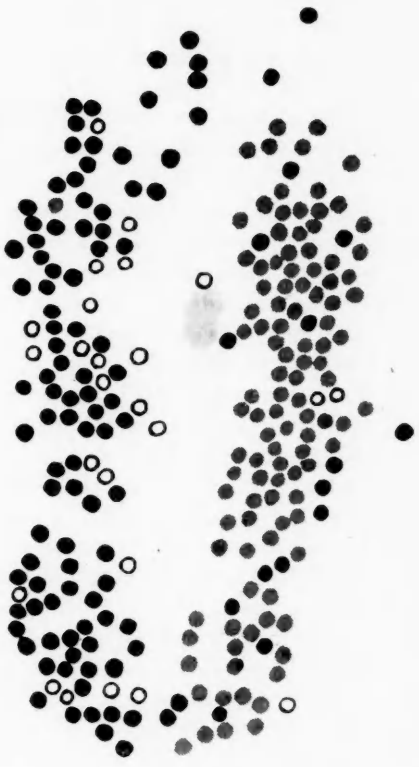

FIG. 13.

FIGS. 11, 12 and 13.—Charts of the distribution of normal and chromatolytic neurones in the oculomotor complex, ten days after intracranial division of the right oculomotor nerve, at the levels of the caudal, middle and upper thirds from left to right. The ventral aspect is below, and at each level there is an interval relatively free of cells between the right and left nuclei, save in fig. 11, where dorsally the caudal central nucleus occupies the midline. Hatched dots indicate chromatolytic neurones, black dots normal cells, and circles cells in the chromophil state. Note the occurrence of chromatolysis in right and left and caudal central nuclei (fig. 11), and the absence of crossed degeneration in the rostral third of the nuclear complex (fig. 13).

RESULTS

In all five of the mid-brains studied after division of the oculomotor nerve unequivocal and widespread retrograde degeneration had occurred. The classical phenomena, including chromatolysis, nuclear eccentricity, and rotundity of the cell body were all noted (figs. 2–4). Of these changes chromatolysis was the most regular and striking. It began

apparently in the perinuclear zone, leaving coarse intact granules at the periphery of the cell (figs. 4 and 5), while in normal oculomotor neurones the same large granules are uniformly distributed through the cytoplasm (figs. 1 and 15). In many neurones all granules had disintegrated into a fine chromatin dust, leaving the cells pale and easily distinguishable even with low powers of the microscope (figs. 3 and 7).

Eccentricity of the nucleus was not always a marked feature, and was occasionally noted in normal cells. The nucleus often appeared rather pale, and the nucleolus somewhat swollen, but these were variable changes. Neurones in a state of distinct chromatolysis were usually rounded and somewhat swollen (fig. 8), but occasionally seemed to preserve their multipolar shape till a late stage. Highly chromatolytic neurones were usually large and irregular in shape, with an indistinct nucleus (fig. 15). From such cells the nucleus was occasionally observed to have been extruded.

Intermediate stages between normal neurones and those showing well-marked chromatolysis appeared to be few, and there was rarely difficulty in deciding between normal and degenerating cells. The state of the granules was taken as the prime criterion, since chromatolysis was by far the most marked and regular change observed. Indeed, other criteria were rarely needed, and neurones which did not display at least a wide zone of disintegrated granules around the nucleus were regarded as unaffected. In the absence of indisputable chromatolysis, nuclear eccentricity and abnormal cell shape were never accepted as indicative of retrograde degeneration.

Every section was examined in all five series, in each of which the oculomotor nuclei appeared through 250–300 sections. Numerous chromatolytic cells were observed in every section, the majority being on the side of the nerve division (figs. 11–13). It was always possible to decide from any section whether the right or left oculomotor nerve had been divided, because of this marked preponderance, but orientation was ensured by cutting a right-angled notch of tissue from the right cerebral peduncle which appeared in every section.

Apart from normal and chromatolytic neurones, a variable number were observed to be in the chromophil state, being shrunken, exaggeratedly multipolar, and very intensely stained throughout the cytoplasm (figs. 2 and 5). Large Nissl granules were usually discernible in such cells (fig. 9), whose cytoplasm stained not only with gallocyanin and other specific chromatin stains, but also with eosin. Cells of like appearance were often noted elsewhere in the mid-brain in areas whence oculomotor fibres are not derived, such as the red nucleus (figs. 9 and 17); and smaller neurones in a similar state were to be found scattered

throughout the reticular formation and central grey substance. They were also observed in the oculomotor nuclei of a normal monkey, and in both red nuclei of an animal submitted to unilateral intra-orbital division of the oculomotor (fig. 6). The neurones of the magnocellular part of the red nucleus were quite often so affected, the change being always bilateral; and in these neurones persistence of large Nissl granules was easily discernible despite the intense coloration of the cytoplasm (fig. 9).

The distribution of normal, chromophil, and chromatolytic neurones was recorded in the case of every tenth section as already described. Every demonstrable motor neurone was recorded save those of the Edinger–Westphal nuclei, upon which it is hoped to make a report at a later date, and the state of each cell was indicated by a different colour (figs. 11 and 13). The permanent spatial records thus prepared were examined and compared. In all cases the general pattern of distribution of chromatolytic neurones was in close agreement, and the findings may be summarized as follows:

(1) Complete counts of normal (including chromophil) and chromatolytic cells through three whole series yielded an average of 42 per cent of cells affected in the total population of the whole oculomotor complex. (Fields in which neurones of the trochlear nucleus were probably present were neglected.) The individual counts were as follows:

	Total normal cells	*Total chromatolytic cells*	*Percentage affected*
Series I	3301	2431	42·2 per cent
„ II	3209	2233	41·0 per cent
„ III	3609	2802	43·7 per cent

(2) At all levels a majority of affected neurones were ipsilateral with respect to the operative lesion. They appeared in the ventral, dorsal, and caudal central nuclei (figs. 11 to 13).

(3) In the caudal two-thirds affected neurones were also observed in the contralateral nuclei.

(4) An average of 10 per cent of the affected neurones were in the contralateral nuclei. The individual counts were as follows:

	Total chromatolytic cells	*Contralateral cells affected*	*Percentage of total*
Series I	2431	222	9·1 per cent
„ II	2233	272	12·1 per cent
„ III	2802	261	8·9 per cent

(5) The proportion of affected neurones in the contralateral nuclei was highest in their lowest third. They were rarely seen in the rostral third of the nuclei (*see* Table and fig. 13).

Complete counts of normal and chromatolytic neurones (ipsilateral and contralateral with respect to nerve division) in every tenth section of Series II, from caudal to rostral extremities.

Level of section	*Normal neurones*	*Chromatolytic neurones*		
		Total	*Ipsilateral*	*Contralateral*
Caudal 1	82	83	60	23
2	79	70	49	21
3	122	73	49	24
4	141	112	90	22
5	174	140	106	34
6	147	118	67	51
7	147	111	93	18
8	145	100	73	27
9	184	91	69	22
10	147	118	90	28
11	102	94	78	16
12	149	102	91	11
13	185	109	99	10
14	178	94	83	11
15	116	75	54	21
16	127	132	119	13
17	168	102	96	6
18	124	108	103	5
19	144	115	114	1
20	127	80	77	3
21	110	64	64	0
22	108	50	50	0
23	97	51	50	1
24	79	38	29	9
25	27	13	13	0

Discussion

The validity of most of the classical work upon the oculomotor nuclei, especially that concerning the possible representation of individual ocular muscles within them, depended upon the production of retrograde degeneration by nerve section. The conclusions of Bernheimer (1897) were based almost entirely upon this method. Its reliability is therefore an issue of crucial importance, especially in view of the value of the monkey as the experimental animal most proximate to man. Warrington (1898), who detected no evidence of chromatolysis after division of the nerve in this animal, has often been quoted. It has not been emphasized, however, that his remarks referred to a single monkey's mid-brain given to him by Sherrington. Further, Warrington reported a diminution in the number of cells on the side of operation, stating also that there were two, equally distributed, types of neurone, the one rather spherical and lightly stained, the other polygonal and deeply stained, remarks which suggest that possibly retrograde changes had, in fact, occurred. Moreover, the monkey had been killed twenty-eight days after nerve section, an important interval, since most observers, including Nissl (1892), have found maximal chromatolysis earlier than this. Furthermore, the occurrence of a considerable degree of recovery of Nissl granules has been noted well before the twenty-eighth day after

section. Nicholson (1923), for example, stated the maximal change to be at fifteen days, and Bucy (1928) found chromatolysis maximal in the rabbit's hypoglossal nucleus at fourteen days, noting also evidence of recovery in many neurones at twenty-one days. Geist (1933) corroborated these findings in the rabbit and reported chromatolysis in the cord of the rhesus monkey 7–10 days after division of the radial and medial nerves. Bodian and Mellors (1945) studied the whole cycle of retrograde degeneration from the first day to the sixth month after section of the monkey's sciatic nerve. They observed maximal changes after 7–15 days, while regeneration of Nissl granules began as early as the third week and was well advanced at twenty-eight days. In view of the above facts the validity of Warrington's observations is open to question.

Nevertheless, these findings do not bear precisely upon the oculomotor neurones of the rhesus monkey; and Bucy (1928) and Geist (1933) have pointed out variation in the rapidity of chromatolysis in different types of neurone and different species. There is merely a consensus of opinion that chromatolysis is well marked in somatic motor neurones by ten days, which was the interval used by Bernheimer (1897), and there is general agreement also that recovery may be well advanced by twenty-eight days. The results of the present study agreed with those of Bernheimer (1897), in so far as extensive chromatolysis was produced with regularity by intracranial division of the oculomotor nerve. Bernheimer (1897), however, based his conception of the internal topography of the nuclei upon the results of intra-orbital section of the branches of the nerve by extirpation of individual ocular muscles. In view of observations of Geist (1933), Bodian and Mellors (1945), and others, that the distance of the division of axons from their cells of origin may affect the degree of chromatolysis, it is perhaps not permissible unreservedly to extend the results of intracranial division of the oculomotor trunk near the mid-brain to more distant interruption of its branches in the orbit. However, as an extension of this work, several intra-orbital divisions have already been carried out, and preliminary examination of this material yields clear evidence of the production of chromatolysis. It is intended to report the results of these additional experiments in the near future.

A few remarks must be added upon the chromophil cells. They were first described by Flesch and Koneff (1886), and Nissl (1894) was also aware of them and of their appearance in normal nervous tissue. They have been variously termed chromophil, pyknomorph, or sclerosed cells. Einarson (1933) has made a special study of chromophily, and he suggested that cells staining thus were in a state of reflex inhibition. In the present study the occurrence of such cells, sometimes in considerable numbers, presented a problem. That they were degenerating cells, due to

division of one nerve or tension upon the other, appeared to be disproved by the occurrence of chromophily in the red nucleus (magnocellular part). Moreover the distribution of such cells was usually uniform in both red nuclei, and the greatest care was taken in all operations to avoid excessive manipulation and stretching. The possibility that the effect was due not to division of axons, but to disturbance of neurones by tension on neighbouring axons, such as those of the oculomotor nerve traversing the red nucleus, appeared improbable, since equal incidence of chromophily in both red nuclei was observed after intra-orbital divisions of a branch of the oculomotor nerve, in which cases tension on either nerve seemed impossible. Furthermore, the occurrence of chromophily elsewhere in the mid-brain has already been noted, and finally, large granules could frequently be discerned in the densely stained cytoplasm of chromophil neurones. Therefore it seemed justifiable to disregard them as evidence of retrograde degeneration, and for the purposes of this study they were regarded as, if not normal neurones, at least not indicative of axonal damage.

As regards the distribution of the changes produced in these experiments, the presence of crossed oculomotor fibres has, of course, long been reported. Gudden (1881) and Spitzka (1888) demonstrated crossed fibres in the rabbit and cat respectively, and Bernheimer (1897) described them in the caudal half of the oculomotor nuclei of the monkey. Little has been said, however, of the proportion and precise nuclear origin of crossed fibres, although Schwabe (1896) regarded them as derived from both the dorsal and ventral nuclei in the dog.

It might be expected that, after section of one oculomotor nerve, approximately half the motor neurones of the combined nuclei of both sides would be affected. Studies on the progress of chromatolysis already mentioned, however, have shown that although a peak in the number of cells affected occurs in a group of neurones after division of their axons, all cells do not synchronize in their response. Even at the time of maximal chromatolysis, some neurones may be too early or too late in the cycle of changes to display undeniable signs of retrograde degeneration. Moreover, in the present study, very exacting standards were observed, and neurones which were probably, but not certainly, affected were deliberately counted as normal. The magnitude of the changes produced, therefore, appeared to be satisfactory, and statistically equivalent to a total response in the cells of origin of the oculomotor nerve after its division.

Conclusions

(a) It is concluded from these observations that the phenomena of retrograde degeneration, in particular chromatolysis, are a reliable indica-

tion of division of the oculomotor nerve in the rhesus monkey. Chromatolysis can regularly be produced and practically all the cells of origin of the divided nerve are affected.

(b) There is evidence that the same conclusions apply to intra-orbital division of branches of the oculomotor nerve.

(c) The pattern of arrangement of the cells of origin of the oculomotor nerve was found to be regular. The pattern indicates a largely ipsilateral origin, but about one-sixth of the axons appear to be derived from the contralateral caudal central dorsal, and ventral nuclei in the caudal two-thirds of the nuclear complex. Rostral to this the fibres appear to be ipsilateral in origin.

Summary

(1) Unilateral intracranial division of the oculomotor nerve was carried out in five rhesus monkeys, which were killed ten to eleven days later.

(2) In every case widespread and marked chromatolysis was noted in the oculomotor neurones.

(3) Examination of serial sections of each mid-brain revealed uniform results throughout the oculomotor nuclei in all cases.

(4) Plotting of the pattern of distribution of chromatolysis upon photographs of every tenth section yielded close agreement in all 5 cases.

(5) The majority of the cells of the ipsilateral nuclei were affected, but in the caudal two-thirds of the oculomotor complex a considerable number of contralateral neurones were affected in the lateral and central nuclei.

(6) Material examined after intra-orbital divisions of oculomotor branches has provided evidence that chromatolysis was also regularly produced in this manner. Further reports upon these experiments will be made at a later date.

Acknowledgments

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REFERENCES

BACH, L. (1899) Sur Lehre von den Angenmuskellähmungen und den Störungen der Pupillenbewegung, *Archiv f. Psychiat.*, **47**, 339–386.

BERNHEIMER, S. (1897) Experminentelle Studien zur Kenntniss der Innervation der inneren und ausseren vom Oculomatorius versorgten Muskeln des Auges, *Archiv. f. Ophth.*, **44**, 481–525.

BODIAN, D., and MELLORS, M. D. (1945) The Regenerative Cycle of Motorneurones, *J. Exp. Medicine*, **81**, 469–488.

BROUWER, B. (1918) Klinisch-anatomisch Untersuchung über den Oculomotoriuskern, *Z. f. d. ges. Neurol. u. Psychiat.*, **40**, 152–193.

BUCY, P. C. (1928) Studies in Degeneration of Peripheral Nerves, *J. Comp. Neurol.*, **45**, 129–159.

CROUCH, R. L. (1936) The Efferent Fibres of the Edinger–Westphal Nucleus, *J. Comp. Neurol.*, **64**, 365–373.

EINARSON, L. (1932) A Method for Progressive Staining of Nissl and Nuclear Material in Nerve Cells, *Amer. J. Pathol.*, **8**, 295–308.

—— (1933) Notes on the Morphology of the Chromophil Material of Nerve Cells and its Relation to Nuclear Substances, *Amer. J. Anat.*, **53**, 141–175.

FLESCH, M., and KONEFF, H. (1886) Bemerkungen uber die Struktur der Ganglienzellen, *Neurol. Centralblatt*, **5**, 145–147.

GEIST, F. D. (1933) Chromatolysis of Efferent Neurones, *Arch. Neurol. and Psychiat.*, **29**, 88–103.

v. GUDDEN, B. (1882) Ueber die Kerne des Angenbewegungsnerven, *Neurol. Centralblatt*, **1**, 9.

NICHOLSON, F. M. (1923) The Changes in Amount and Distribution of the Iron-containing Protein of Nerve Cells Following Injury to Their Axons, *J. Comp. Neurol.*, **36**, 37–77.

NISSL, F. (1892) Über die Veränderungen der Ganglienzellen am Facialiskern des Kanichens nach Ausreissung der Nerven, *Allg. Z. Psychiat.*, **48**, 197–198.

—— (1894) Mitteilungen zur Anatomie der Nervenzellen, *Allg. Z. Psychiat.*, **50**, 370.

SCHWABE, H. (1896) Ueber die Gliederung des Oculomotoriushauptkerns, *Neurol. Centralblatt*, **15**, 792–794.

SPITZKA, F. C. (1888) The Oculomotor Centres and their Co-ordinators, *J. Nerv. Ment. Dis.*, **13**, 413–432.

WARRINGTON, W. B. (1898) On the Structural Alterations Observed in Nerve Cells, *J. Physiol.*, **23**, 112–129.

LEGENDS FOR PLATES

PLATE XXVI

FIG. 1.—Normal multipolar neurones from the oculomotor nucleus of an unoperated monkey. Note central nucleus, large, flaky granules and polygonal form. Gallocyanin. × 420.

FIG. 2.—Cells of left oculomotor nucleus ten days after intracranial division of left oculomotor nerve. Above are two unaffected neurones. The rounded cell, with eccentric nucleus, is degenerating, and shows only one or two peripheral granules, the remainder having disintegrated into a fine dust. The lower cells are chromophilic. Note their darkly stained, shrunken appearance. Gallocyanin. × 420.

FIG. 3.—Advanced chromatolysis in neurons of the left dorsal nucleus, eleven days after division of the left oculomotor nerve. Note eccentric nuclei and absence of normal large granules, which are replaced by a fine chromatin dust. Gallocyanin. × 420.

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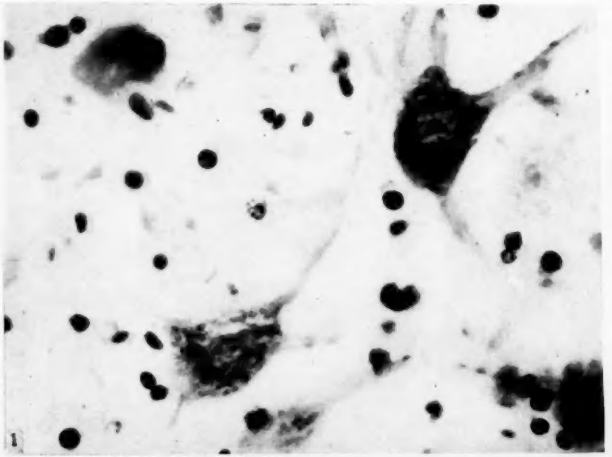

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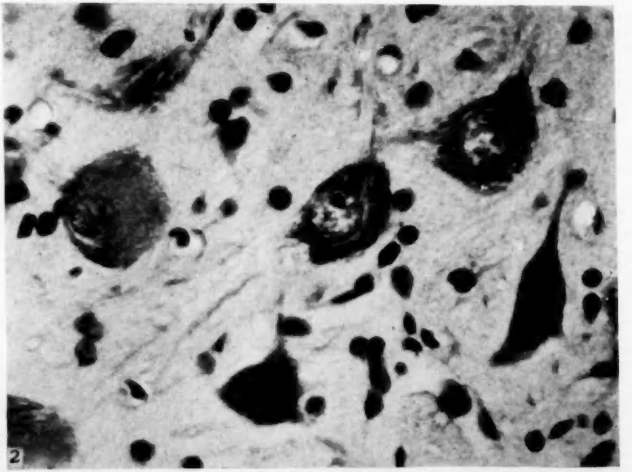

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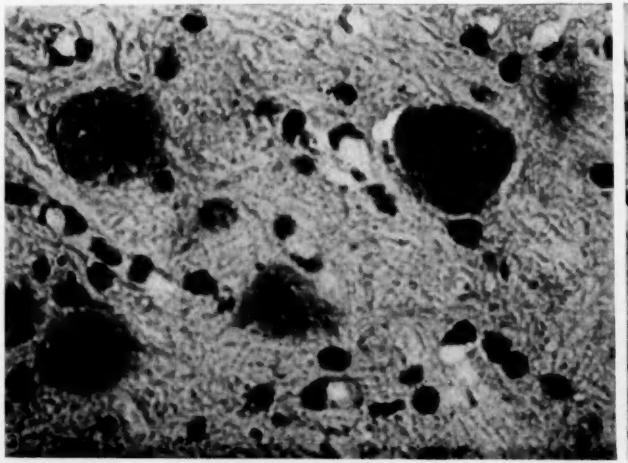

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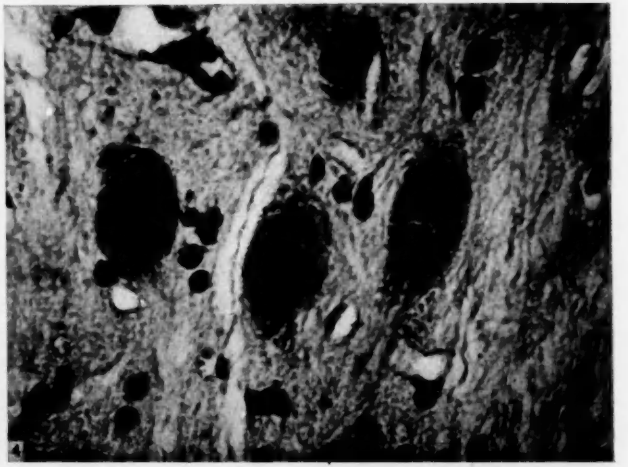

To illustrate article by R. Warwick.

PLATE XXVII

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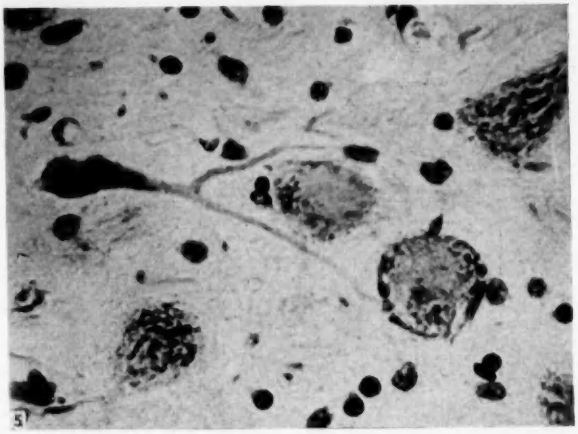

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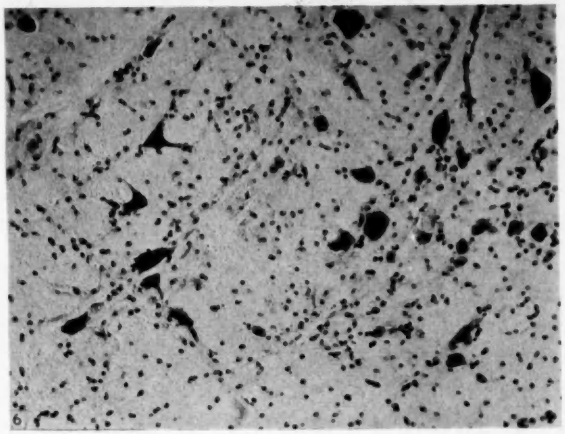

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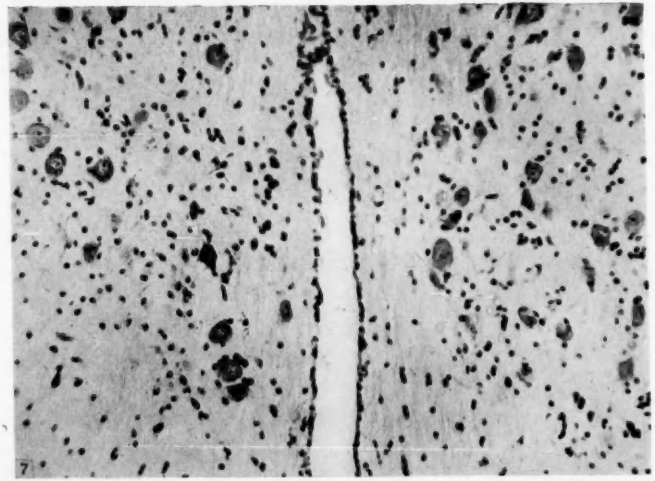

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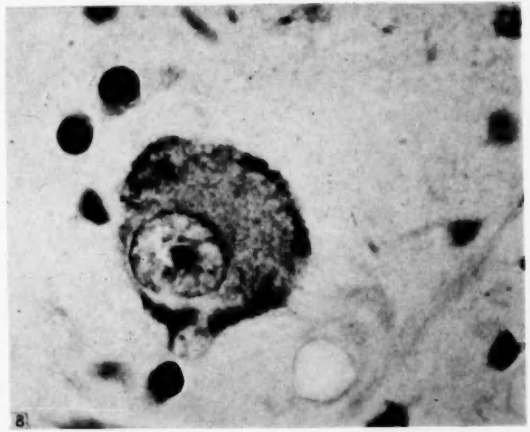

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PLATE XXVIII

FIG. 9

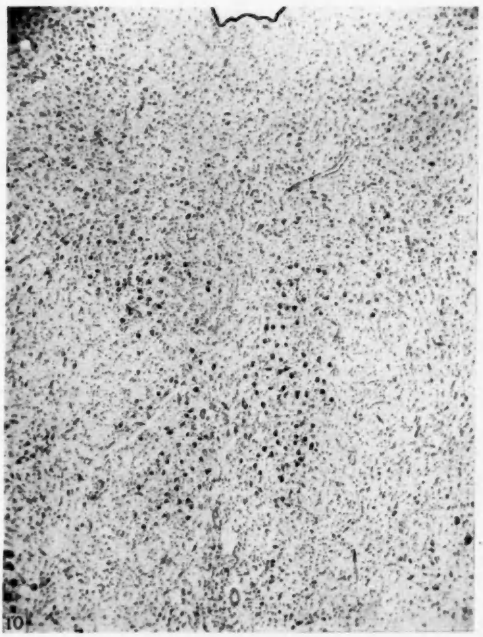

FIG. 10

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PLATE XXIX

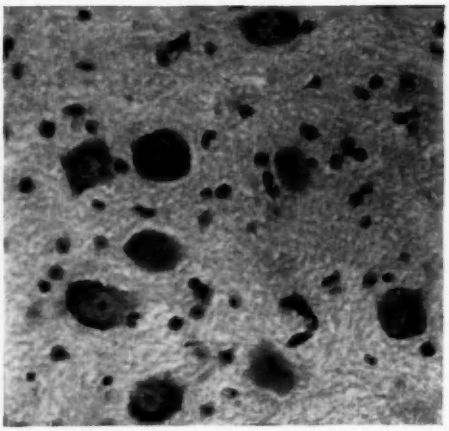

FIG. 14

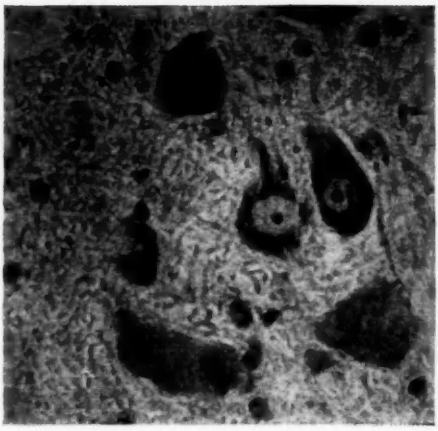

FIG. 15

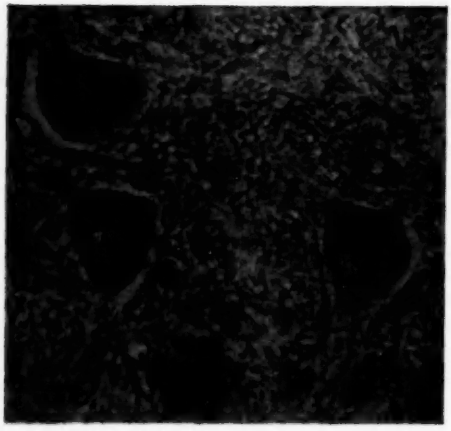

FIG. 16

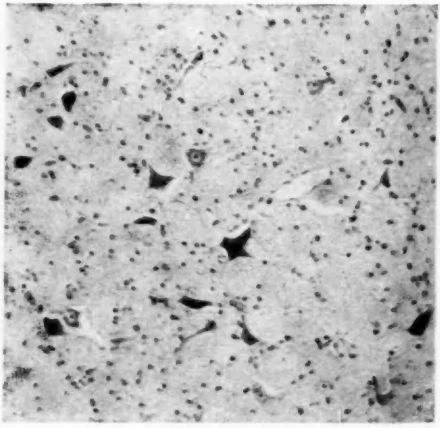

FIG. 17

To illustrate article by R. Warwick.

FIG. 4.—Three motor neurones of the left oculomotor nucleus, eleven days after section of the left nerve. The cell on the right is apparently unaffected, that on the left is at an early stage of degeneration (note peripheral persistence of large granules), while the middle cell is at a later stage of chromatolysis (note almost complete disintegration of granules into a fine dust). Gallocyanin. × 420.

PLATE XXVII

FIG. 5.—Oculomotor neurones eleven days after nerve section. Centrally are two chromatolytic neurones. To the left is a chromophil cell. The remaining two motor neurones are apparently normal. Gallocyanin. × 420.

FIG. 6.—Neurones of the right red nucleus (magnocellular part), eleven days after extirpation of the inferior oblique muscle in the left orbit. Note that many of the cells are in the chromophil state. Borrel's methylene blue. × 100.

FIG. 7.—Field in a transverse section through the middle third of the oculomotor nuclei, eleven days after intracranial division of the right oculomotor nerve. The vessel seen cut longitudinally separates the ventral parts of the right and left nuclei. Note many neurones with normal Nissl granules on the left, and also rounded, pale, chromatolytic neurones on both sides, but in preponderance on the right. Gallocyanin. × 100.

FIG. 8.—Highly magnified view of a degenerating multipolar neurone of the oculomotor nucleus, ten days after ipsilateral intracranial division of the oculomotor nerve. Note the rounded form, eccentric nucleus, and breaking of Nissl granules into fine dust save at the periphery of the cell. Gallocyanin. × 1000.

PLATE XXVIII

FIG. 9.—Normally staining and chromophilic neurones of the magnocellular part of the red nucleus, ten days after intracranial division of the nerve to the inferior oblique muscle. Note that, in the chromophil cell on the left, Nissl granules are discernible in the densely stained cytoplasm. Gallocyanin. × 750.

FIG. 10.—Transverse section of the mid-brain of a rhesus monkey showing the whole oculomotor complex ventral to the aqueduct. Note that the individual motor neurones stand out quite clearly and can easily be identified under the microscope in the corresponding section. Gallocyanin. × 30.

PLATE XXIX

FIG. 14.—Normal and chromatolytic neurones of the oculomotor nucleus ten days after nerve division. Note pallor of chromatolytic cells, in three of which large peripheral granules are still present. Two normal neurones are seen, at the upper and lower limits of the field. Gallocyanin. × 300.

FIG. 15.—Field in oculomotor nucleus ten days after extirpation of the contralateral inferior oblique muscle in the orbit. Three normal neurones are seen above and two chromatolytic neurones below. Borrel's methylene blue. × 300.

FIG. 16.—Four chromatolytic neurones from the same experiment as fig. 15. Note disappearance of granules from all except one cell, in which a few persist at the periphery. The nuclei are not markedly eccentric. Borrel's methylene blue. × 300.

FIG. 17.—Neurones of the magnocellular part of the red nucleus eleven days after contralateral division of the whole oculomotor nerve. The pink stained cells are in the chromophil state. Granules can still be seen in them, however. The cytoplasm of the normal cells does not take up eosin, and the granules are more distinct. Gallocyanin and eosin. × 100.

Notices of Recent Publications

A Cytoarchitectonic Atlas of the Rhombencephalon of the Rabbit. By H. Muessen and J. Olszewski. 1949. Pp. 52 with 15 large plates. S. Karger. Basel and New York: Price 50 Swiss francs.

This beautiful atlas of the rhombencephalon of the rabbit has been produced by two students of the Vogts, and is intended to supplement and bring up to date the standard atlas of Winkler and Potter as an aid to experimental investigations. Except for the first and last plates, which are taken from sections stained for myelin, all the plates are made from sections stained for Nissl granules, and comprise (1) a × 40 magnification of half the transverse section of the brain-stem, (2) one or more general views of individual nuclei × 200, and (3) one or more photomicrographs of single nerve cells × 1,000. With the magnification used and the excellence of the reproduction it is possible to see every nerve cell in the complete hemisection, and the ratio of larger to smaller forms and the exact appearance of some of the larger cells are shown by the higher magnifications. The outlining and lettering of the various nuclei and their subdivisions is clear and the letterpress, which is in both German and English, is terse and simple. A synopsis of the individual nuclei at the end of the atlas facilitates its use but there is no alphabetical index.

The atlas should prove to be of great value to physiologists and pharmacologists, but neurologists may regret that so much trouble and expense have been devoted to the brain-stem of the rabbit when a cytological atlas of the human brain-stem is so badly needed. It is to be hoped that one or both of the authors may, before long, be able to supply this want.

External Morphology of the Primate Brain. By Cornelius J. Connolly. Pp. 378, with 334 illustrations in the text. Springfield: C. C. Thomas. Price not stated.

This scholarly monograph is based on the study of a large number of brains of monkeys, apes and men. In many cases where he has used museum specimens, the author has only been able to examine the outer surface of the brain and for this reason the mesial surface and the inferior surface of the occipital lobes receive little consideration. They present, however, fewer problems, at least in the subhuman species, and have a more constant fissural pattern than the convexity, so that this gap in the author's study of the subject is of minor importance.

The study appears to have been undertaken for its own sake, but it has several obvious correlations and practical applications in which the neurologist is specially interested. The first is the relationship of the sulci in the lower monkeys to those in the higher apes and in man. The author finds many errors of interpretation of this relationship in the older literature and the study he has made of many specimens of many species and subspecies should do much to solve this problem. The allied problem of the relationship of sulci to cortical areas is one in which experimentalists have a special interest. Here we find much less constancy than we might expect, except in the case of a few primary sulci such as the *calcarine, callosomarginal* and *central.* Even so constant a fissure as the *sulcus lunatus* does not sharply outline the *area striata* in all species. The author points out that the sulci are determined by intrinsic hereditary factors, and the stresses which le Gros

Clark has postulated as developing between the growing brain and the firm skull have little influence on them except, perhaps, in determining their depth. There is little doubt that the line of transition from the neuronal pattern of one cortical area to that of its neighbour may determine the position of a sulcus, probably by forming a division between two areas of expanding growth, but as von Economo has pointed out, the transition from one cortical pattern to another may be gradual or may take place on the surface or the wall of a convolution, and in the transition from a simple to a more complex fissura pattern the relationship of sulci to cortical areas becomes blurred.

Another important application of the present study is to the interpretation of endocranial casts of fossil skulls and the determination of their evolutionary stage. The author devotes two long chapters to this subject, concluding that *pithecanthropus* and *sinanthropus* were definitely human, as their fissural pattern shows a much closer relationship to that of present day man than to any subhuman form.

The author gives a valuable summary of the work which has been done on encephalometry and suggests a more practical method for future study.

Chapter III is devoted to the development of fissures in man. This is based on a considerable new material and the size and stage of development of the brains is related to length of pregnancy in weeks rather than to the crown-rump length which is confusing owing to its variation in different specimens and in different races. This study will be of great value in interpreting development abnormalities of the cortex and in assessing the age of a fœtus.

A full index and an extensive bibliography add to the value of the book as a work of reference.

Human Personality and its Minor Disorders. By WILLIAM HARROWES. 1949. Pp. viii plus 260. Edinburgh: E. and S. Livingstone, Ltd. Price 15s.

The teaching of Adolf Meyer has had a larger effect on psychiatry in Britain than in the lands either of his birth or of his adoption. The common-sense approach which it inspires is, it seems, naturally found sympathetic by British psychiatrists, whereas psychiatry in Switzerland is still largely dominated by the teaching of Kraepelin and of Bleuler, and in the United States it has become but one of the domains of psychoanalysis. But while current English textbooks are considerably influenced by Meyer, Dr. Harrowes's work is the first to appear which from beginning to end is wholly Meyerian. Perhaps wisely, the subject matter is limited to those fields in which the Meyerian formulation is most valuable and most acceptable, i.e. the development of the personality and the clinical aspect of psychological reactions; and the organic and endogenous psychoses, which can only be forced with difficulty into Meyer's scheme, are left out of account.

One of Meyer's principal contributions to teaching was to devise a plan for case-taking, a plan so elaborate that many days could be spent in filling out its details after discussion with the patient. The plan provides the frame-work of this textbook, and the questions it asks are the sub-titles of the discussion. The numerous modes of emotional reaction to difficulties become comprehensible in this way, and the student and the general practitioner will find their understanding of individual patients with minor neurotic disorders or psychosomatic complaints considerably eased by following the precepts very lucidly presented by the author. For the psychiatrist and the neurologist, however, corresponding defects must be emphasized. The understanding gained tends to be superficial, and events which are essentially pathological cannot be understood in this way at all. So it is that we miss, for instance, in the section on hysteria, any discussion of the important relation between hysterical symptoms and organic lesions of the brain. The major themes of psychiatry cannot be covered by common sense, however erudite.

A Text-Book of Psychiatry. By Sir David Henderson and the late R. D. Gillespie, Seventh Edition. 1950. Pp. xii, 740. Geoffrey Cumberlege, Oxford University Press, London, New York, Toronto. Price 32s. 6d.

No very great changes have been made in the last edition of this standard work, the principal one being the re-writing of the chapter on Psychopathic States. In this field Professor Henderson has himself made a noteworthy contribution. He takes the view, which is strongly contested by other authors, that "psychopathic states are as specific as any other psychiatric entities." Their definition is to a large extent negative, but in so far as they can be positively qualified Professor Henderson defines the psychopathic individual as one who has been habitually abnormal from youth, rebellious, individualistic, psychologically immature and emotionally unstable. He does not adapt to his social milieu, lacks judgment, foresight and ordinary prudence, and fails to profit from experience. Yet it is not maintained that other psychopathic types cannot be described, or that all the features of personality mentioned are always shown. It is not possible to make any statement, which would comprehend all varieties of psychopathy, about ætiology or prognosis. In fact, the attempt to describe psychopathic states as a clinical syndrome leads to as many difficulties as it avoids; and the reader is left to wonder why Professor Henderson finds it necessary to postulate any specificity. Nevertheless the classification of psychopathic states into three main types, the predominantly aggressive, the predominantly inadequate, and the predominantly creative, has been found by other writers to provide a useful frame of reference; and the clinical description within its self-imposed limits is just and informative.

Little comment on the rest of this well-known book is required. It has the merits of previous editions, as also the deficiencies, many of which can be traced to the disputability of the tenets and the lack of preciseness of the subject matter of psychiatry itself.

Clinical Electroencephalography. By Robert Cohn. 1949. London: McGraw-Hill Book Company, Inc. Price 119s.

This large volume is really an atlas, and is in no sense a textbook. Only the first 20 or so of the 640 pages deal with the physics and technique of electroencephalography, and its physiology is not considered at all. On each pair of pages a clinical abstract and summary description of the electroencephalogram faces samples of records taken from a single patient—and so for nearly 300 patients. These examples are grouped under headings, so that head injuries, for instance, appear consecutively, but a series of electroencephalograms from patients with headaches seems to carry illustrations too far. Beyond his descriptive grouping Dr. Cohn has undertaken little scientific synthesis, and beyond a list of ten unrepresentative references at the end there is no attempt to relate the mass of his material to the experience and conclusions of other workers. Anyone who wishes to embark on the clinical interpretation of electroencephalographic records must do so in the laboratory, from patients studied by himself; access to Dr. Cohn's personal experience is a very poor substitute. To have to pay 119 shillings to gain it is a salutary deterrent.

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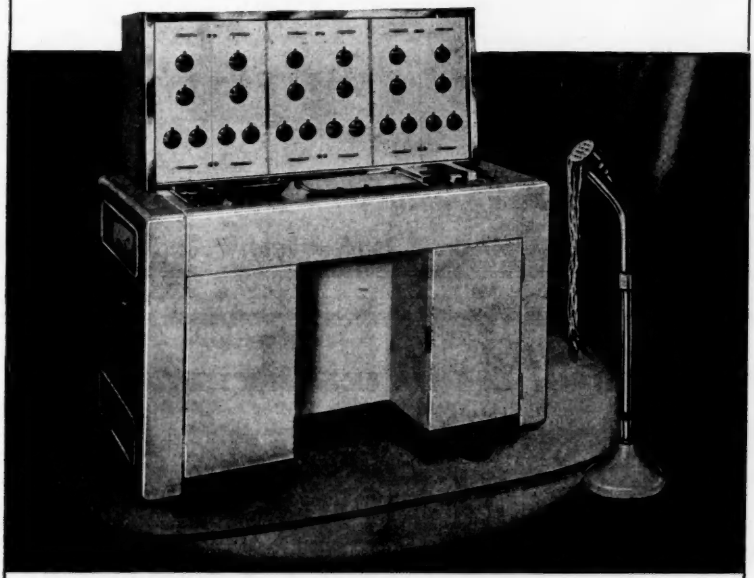

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INDEX

TO

BRAIN:

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VOL. LXXIII, 1950

AUTHORS

PAGE

Allison, R. S.
Survival in Disseminated Sclerosis: A Clinical Study of a Series of Cases First Seen Twenty Years Ago 103

Beck, E.
The Origin, Course and Termination of the Prefronto-Pontine Tract in the Human Brain 368

Bowden, R. E. M., and Sholl, D. A.
The Advance of Functional Recovery after Radial Nerve Lesions in Man 251

Brain, W. Russell
The Cerebral Basis of Consciousness 465

Brain, W. Russell, and Greenfield, J. G.
Late Infantile Metachromatic Leuco-Encephalopathy, with Primary Degeneration of the Interfascicular Oligodendroglia 291

Campbell, A. M. G., Herdan, G., Tatlow, W. F. T., and Whittle, E. G.
Lead in Relation to Disseminated Sclerosis 52

Cobb, W., and Hill, D.
Electroencephalogram in Subacute Progressive Encephalitis 392

Cumings, J. N.
The Chemistry of Cerebral Cysts 244

Ethelberg, S.
Symptomatic "Cataplexy" or Chalastic Fits in Cortical Lesion of the Frontal Lobe 499

Gellhorn, E.
The Validity of the Concept of Multiplicity of Representation in the Motor Cortex under Conditions of Threshold Stimulation 267

Gellhorn, E., and Johnson, D. A.
Further Studies on the Role of Proprioception in Cortically Induced Movements of the Foreleg in the Monkey 513

Gellhorn, E., and Johnson, D. A.
The Specificity of the Electromyographic Method for the Investigation of the Motor Cortex 275

Greenfield, J. G.
Encephalitis and Encephalomyelitis in England and Wales During the Last Decade 141

PAGE

Greenfield, J. G., and Brain, W. Russell
Late Infantile Metachromatic Leuco-Encephalopathy, with Primary Degeneration of the Interfascicular Oligodendroglia 291

Hawkins, R., White, J. C., Sweet, W. H., and Nilges, R. G.
Anterolateral Cordotomy: Results, Complications and Causes of Failure 346

Herdan, G., Campbell, A. M. G., Tatlow, W. F. T., and Whittle, E. G.
Lead in Relation to Disseminated Sclerosis 52

Hill, D., and Cobb, W.
Electroencephalogram in Subacute Progressive Encephalitis 392

Hinshaw, J. R., and Sinclair, D. C.
A Comparison of the Sensory Dissociation Produced by Procaine and by Limb Compression 480

Hinshaw, J. R., and Sinclair, D. C.
Sensory Changes in Procaine Nerve Block 224

Johnson, D. A., and Gellhorn, E.
Further Studies on the Role of Proprioception in Cortically Induced Movements of the Foreleg in the Monkey 513

Johnson, D. A., and Gellhorn, E.
The Specificity of the Electromyographic Method for the Investigation of the Motor Cortex 275

Joiner, C. L., McArdle, B., and Thompson, R. H. S.
Blood Pyruvate Estimations in the Diagnosis and Treatment of Polyneuritis 431

Kaplan, L., and Kennedy, F.
The Effect of Head Posture on the Manometrics of the Cerebrospinal Fluid in Cervical Lesions: A New Diagnostic Test 337

Kendall, D.
Non-Penetrating Injuries of the Median Nerve at the Wrist 84

Kennedy, F., and Kaplan, L.
The Effect of Head Posture on the Manometrics of the Cerebrospinal Fluid in Cervical Lesions: A New Diagnostic Test 337

Kuhn, R. A.
Functional Capacity of the Isolated Human Spinal Cord 1

Lassek, A. M.
The Human Pyramidal Tract. XVIII: An Analysis of its Pathophysiological Status 95

Liddell, E. G. T., and Phillips, C. G.
Thresholds for Cortical Representation 125

Maas, O., and Paterson, A. Spencer
Myotonia Congenita, Dystrophia Myotonica and Paramyotonia: Reaffirmation of their Identity 318

McArdle, B., Joiner, C. L., and Thompson, R. H. S.
Blood Pyruvate Estimations in the Diagnosis and Treatment of Polyneuritis 431

McFie, J., Piercy, M. F., and Zangwill, O. L.
Visual-Spatial Agnosia Associated with Lesions of the Right Cerebral Hemisphere 167

Martin, J. Purdon
Fits of Laughter (Sham Mirth) in Organic Cerebral Disease 453

Nilges, R. G., White, J. C., Sweet, W. H., and Hawkins, R.
Anterolateral Cordotomy: Results, Complications and Causes of Failure 346

O'Connell, J. E. A., and Turner, J. W. Aldren
Basilar Impression of the Skull 405

PAGE

Parsons-Smith, G., and Williams, D.
Cortical Rhythms Not Seen in the Electroencephalogram 191
Paterson, A. Spencer, and Maas, O.
Myotonia Congenita, Dystrophia Myotonica and Paramyotonia: Reaffirmation of their Identity 318
Phillips, C. G., and Liddell, E. G. T.
Thresholds for Cortical Representation 125
Piercy, M. F., McFie, J., and Zangwill, O. L.
Visual-Spatial Agnosia Associated with Lesions of the Right Cerebral Hemisphere 167
Reinhold, M.
A Case of Auditory Agnosia 203
Sholl, D. A., and Bowden, R. E. M.
The Advance of Functional Recovery after Radial Nerve Lesions in Man 251
Sinclair, D. C., and Hinshaw, J. R.
A Comparison of the Sensory Dissociation Produced by Procaine and by Limb Compression 480
Sinclair, D. C., and Hinshaw, J. R.
Sensory Changes in Procaine Nerve Block 224
Stern, W. E.
The Lumbar Cerebrospinal Fluid Protein in Intracranial Meningiomas 72
Sweet, W. H., White, J. C., Hawkins, R., and Nilges, R. G.
Anterolateral Cordotomy: Results, Complications and Causes of Failure 346
Tatlow, W. F. T., Campbell, A. M. G., Herdan, G., and Whittle, E. G.
Lead in Relation to Disseminated Sclerosis 52
Thompson, R. H. S., Joiner, C. L., and McArdle, B.
Blood Pyruvate Estimations in the Diagnosis and Treatment of Polyneuritis 431
Turner, J. W. Aldren, and O'Connell, J. E. A.
Basilar Impression of the Skull 405
Warwick, R.
A Study of Retrograde Degeneration in the Oculomotor Nucleus of the Rhesus Monkey, With a Note on a Method of Recording its Distribution 532
White, J. C., Sweet, W. H., Hawkins, R., and Nilges, R. G.
Anterolateral Cordotomy: Results, Complications and Causes of Failure 346
Whittle, E. G., Campbell, A. M. G., Herdan, G., and Tatlow, W. F. T.
Lead in Relation to Disseminated Sclerosis 52
Williams, D., and Parsons-Smith, G.
Cortical Rhythms Not Seen in the Electroencephalogram 191
Zangwill, O. L., McFie, J., and Piercy, M. F.
Visual-Spatial Agnosia Associated with Lesions of the Right Cerebral Hemisphere 167

SUBJECTS

Auditory Agnosia, A Case of. M. Reinhold 203
Basilar Impression of the Skull. J. E. A. O'Connell and J. W. Aldren Turner 405
Blood Pyruvate Estimations in the Diagnosis and Treatment of Polyneuritis. C. L. Joiner, B. McArdle and R. H. S. Thompson 431
"Cataplexy," Symptomatic, or Chalastic Fits in Cortical Lesion of the Frontal Lobe. Sven Ethelberg 499
Cerebral Basis of Consciousness, The. W. Russell Brain 465

PAGE

Cerebral Cysts, The Chemistry of. J. N. Cumings 244

Cordotomy, Anterolateral: Results, Complications and Causes of Failure. J. C. White, W. H. Sweet, R. Hawkins and R. G. Nilges 346

Cortical Representation, Thresholds for. E. G. T. Liddell and C. G. Phillips 125

Cortical Rhythms not seen in the Electroencephalogram. D. Williams and G. Parsons-Smith 191

Disseminated Sclerosis, Lead in Relation to. A. M. G. Campbell, G. Herdan, W. F. T. Tatlow and E. G. Whittle 52

Disseminated Sclerosis, Survival in: A Clinical Study of a Series of Cases First Seen Twenty Years Ago. R. S. Allison 103

Effect, The, of Head Posture on the Manometrics of the Cerebrospinal Fluid in Cervical Lesions: A New Diagnostic Test. Lawrence Kaplan and Foster Kennedy 337

Electroencephalogram in Subacute Progressive Encephalitis. William Cobb and Denis Hill 392

Electromyographic Method for the Investigation of the Motor Cortex, The Specificity of the. E. Gellhorn and D. A. Johnson 275

Encephalitis and Encephalomyelitis in England and Wales During the last Decade. J. G. Greenfield 141

Fits of Laughter (Sham Mirth) in Organic Cerebral Disease. J. Purdon Martin 453

Functional Recovery after Radial Nerve Lesions in Man, The Advance of. R. E. M. Bowden and D. A. Sholl 251

Late Infantile Metachromatic Leuco-Encephalopathy, with Primary Degeneration of the Interfascicular Oligodendroglia. W. Russell Brain and J. G. Greenfield 291

Lumbar Cerebrospinal Fluid Protein in Intracranial Meningiomas, The. W. E. Stern 72

Median Nerve, Non-Penetrating Injuries of, at the Wrist. David Kendall 84

Multiplicity of Representation in the Motor Cortex under Conditions of Threshold Stimulation, The Validity of the Concept of. E. Gellhorn 267

Myotonia Congenita, Dystrophia Myotonica and Paramyotonia: Reaffirmation of their Identity. Otto Mass and A. Spencer Paterson 318

Prefronto-Pontine Tract in the Human Brain, The Origin, Course and Termination of the. Elisabeth Beck 368

Proprioception in Cortically Induced Movements of the Foreleg in the Monkey, Further Studies on the Role of. E. Gellhorn and D. A. Johnson 513

Pyramidal Tract, The Human. XVIII: An Analysis of its Pathophysiological Status. A. M. Lassek 95

Retrograde Degeneration in the Oculomotor Nucleus of the Rhesus Monkey, A Study of; With a Note on a Method of Recording its Distribution. R. Warwick 532

Sensory Changes in Procaine Nerve Block. D. C. Sinclair and J. R. Hinshaw 224

Sensory Dissociation Produced by Procaine and by Limb Compression, A Comparison of the. D. C. Sinclair and J. R. Hinshaw 480

Spinal Cord, Functional Capacity of the Isolated Human. R. A. Kuhn ... 1

Visual-Spatial Agnosia Associated with Lesions of the Right Cerebral Hemisphere. J. McFie, M. F. Piercy and O. L. Zangwill 167

Notices of Recent Publications 121, 280, 427, 544

PAGE

NOTICES OF RECENT PUBLICATIONS

Clinical Electroencephalography. R. Cohn 547
Etudes Psychiatriques: Historique — Méthodologie — Psychopathologie Générale. Henry Ey 280
External Morphology of the Primate Brain. C. J. Connolly 544
Psycho-Analysis. A Handbook for Medical Practitioners and Students of Comparative Psychology. E. Glover 428
Psychological Aspects of Clinical Medicine. S. B. Hall 280
Human Personality and Its Minor Disorders. W. Harrowes 545
A Text-Book of Psychiatry. Sir D. Henderson and the late R. D. Gillespie 546
Cerebral Angiography. P. Almeida Lima 546
Selective Partial Ablation of the Frontal Cortex. By the Columbia-Greystone Associates. Edited by F. A. Mettler 427
A Cytoarchitectonic Atlas of the Rhombencephalon of the Rabbit. H. Muessen and J. Olszewski 544
Perspectives in Neuropsychiatry. Essays Presented to Professor F. L. Golla. Edited by D. Richter 122
Observations on the Pathology of Hydrocephalus. D. S. Russell 121